ORIGINAL ARTICLE

The Clinical Impression of NDM-producing *Acinetobacter baumannii* in Intensive Care Units of the University Referral Hospital in North India

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Abstract

Aims and background: Carbapenem-resistant *Acinetobacter baumannii* (CRAb), a major public health threat, causes severe infections in Intensive Care Unit (ICU) patients. It resists β-lactam antibiotics through mechanisms like New Delhi metallo-beta-lactamase (NDM).

Materials and methods: In ICU patients, 69 *Acinetobacter* species were isolated from 86 non-fermenting Gram-negative bacilli. Isolates were identified using biochemical methods and Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (MS), and carbapenem resistance detection was done by both phenotypic (mCIM and eCIM) and molecular methods.

Results: Out of 66 *A. baumannii*, 61 were carbapenem-resistant, with 20 confirmed as NDM producers. NDM-positive isolates exhibited higher resistance and were associated with significant mortality (75%).

Conclusion: NDM-positive *Acinetobacter* isolates are significant ICU pathogens with poor outcomes. Key risk factors include prolonged ICU stays, prior antimicrobial use, and inadequate therapy. Early detection and infection control are crucial.

Clinical significance: NDM-positive *Acinetobacter* infections in ICU patients are linked to poor outcomes, highlighting the need for early detection and control measures.

Keywords: Antimicrobial resistance, Bloodstream infection, Carbapenem-resistant *Acinetobacter baumannii*, Intensive care unit, New Delhi metallo-β-lactamases.

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Highlights

Treating bloodstream infections in Intensive Care Unit (ICU) patients, especially those caused by metallo-β-lactamases (NDM)-positive *Acinetobacter*, is challenging because of their resistance patterns. Extended stays in the ICU, previous administration of antibiotics, and insufficient early treatment all contribute to unfavorable outcomes. Efficient management requires timely identification, control of infections, and tailored antimicrobial treatment plans to minimize occurrence and mortality.

Introduction

Carbapenem-resistant *Acinetobacter baumannii* (CRAb) is a major public health threat, and it is considered one of the top-priority pathogens (WHO).[1] Carbapenem-resistant *A. baumannii* frequently causes infections in people who have been cared for in hospital facilities, particularly those who require invasive medical devices in intensive care units. In India, CRAb continues to be a major cause of morbidity in healthcare facilities, including bloodstream infections, ventilator-associated pneumonia (VAP), device-associated infections (DAI), wound or skin and soft-tissue infections (SSTI), urinary tract infections (UTI), intra-abdominal infection (IAI), and meningitis.[2] The mechanisms of antibiotic resistance in *Acinetobacter* spp. are diverse. There are several reasons why some bacteria become resistant to β-lactam medicines. These include making more β-lactamase, having too many efflux pumps, and having less permeable outer membranes. But making too many carbapenem-hydrolyzing enzymes is still a big problem. *Acinetobacter* species usually become resistant to carbapenems by making NDM and oxacillinase-type carbapenemases.[3] The novel NDM known as New Delhi metallo-β-lactamases (blaNDM-1) exhibit a high resistance to nearly all β-lactam antibiotics. Carbapenems are a crucial antimicrobial agent against NDM producers.[4] In addition, NDM and other NDM like IMP and VIM have also been reported in CRAb.[5] Carbapenem-resistant *A. baumannii* isolates have limited treatment options because of their widespread resistance to several antimicrobial drugs, including polymyxins, in addition to their resistance to carbapenem.[6] Many countries, including China, the Middle East, Europe, the USA, and the Indian subcontinent, have reported

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infrequent cases of NDM-producing *A. baumannii* (NDMAb). Despite the ubiquitous presence of NDMAb, less is known regarding its epidemiology, clinical characteristics of infected patients, and transmission networks in hospital settings.[7,8] The study aimed to identify potential risk factors and correlations between *A. baumannii*'s NDM gene presence and antimicrobial resistance in university hospitals ICU patients with bacteremia.

Materials and Methods

A total of 69 isolates of *Acinetobacter* species were obtained from patients whose blood culture was positive for non-fermenting Gram-negative bacilli (GNNFB) isolates admitted in various ICUs and enrolled in this hospital-based observational study of King George's Medical University, India. The study was conducted from September 2020 to October 2021 and was approved by the institutional ethics committee of King George's Medical University, Lucknow (Ref No: 102nd ECM II B Thesis/P42). Informed written consent was obtained from all participants. This study included all ICU patients with bacteriemia that were confirmed by positive blood culture. Clinical details regarding demographic data, occupation, residential address, nature of work, history of previous hospitalization due to medical and surgical illness, duration of ICU admission, duration of subjection of antimicrobials, and any invasive procedure during ICU stay were collected.

Bacterial Isolates and Antimicrobial Susceptibility Tests

A total of 69 *Acinetobacter* species isolates were isolated from 86 non-fermenting GNNFB isolates from blood specimens collected from patients admitted in the ICU of the university hospital. The isolates were identified by conventional biochemical methods and MALDI-TOF. The Kirby–Bauer disc diffusion method was used to test all isolates for carbapenem resistance as per the Clinical and Laboratory Standards Institute recommendation 2020.[9,10] The Kirby–Bauer disk diffusion method was performed with the following antibiotics: Piperacillin-tazobactam (10 µg), ceftazidime (30 µg), cefepime (30 µg), imipenem (10 µg), meropenem (10 µg), gentamicin (10 µg), tobramycin (10 µg), amikacin (30 µg) ciprofloxacin (5 µg), levofloxacin (5 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg). The minimum inhibitory concentration (MICs) of colistin were determined using the broth microdilution method as per CLSI recommendations. The breakpoints of colistin were as follows: isolates with MICs of 2–4 mg/mL were categorized as intermediate, and those with MICs of >4 mg/mL were categorized as resistant. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality controls. All these strains were tested for susceptibility to meropenem (10 µg, Hi-media) by the disc diffusion method, and strains that showed reduced susceptibility to meropenem were further confirmed for carbapenem resistance by MICs for meropenem, obtained with the VITEK COMPACT 2MS system. Resistance of *Acinetobacter* species strains to carbapenem was reported if the MIC to meropenem was ≥16 µg/mL, possibly carbapenemase producers, and was characterized with both phenotypic as well as molecular tests for detection of carbapenemase.[10]

Phenotypic Test for Detection of Carbapenemase

A phenotypic detection test for OXA-48-like carbapenemases and Ambler classes A and B, known as the mCIM test, was conducted on all isolates of Acetobacter species. The eCIM phenotypic test was only performed on isolates that tested positive for the mCIM test, following the guidelines set by the Clinical and Laboratory Standard Institute (CLSI) in 2020.[10]

Table 1: Details of primers utilized in this study

Primer name	*Primer sequence*	*PCR product size*
VIM-F	GATGGTGTTTGGTCGCATA	390 bp
VIM-R	CGAATGCGCAGCACCAG	
IMP-F	GGAATAGAGTGGCTTAAYTCTC	232 bp
IMP-R	CCAAACYACTASGTTATCT	
NDM-F	CACCTCATGTTTGAATTCGCC	984 bp
NDM-R	NDMr CTCTGTCACATCGAAATCGC	

Molecular Investigations for Detection of Drug-resistant Genes (DNA Extraction and PCR for Carbapenemase Genes)

The most prevalent and clinically pertinent metallo beta-lactamases, New Delhi metallo-beta-lactamase (NDM), verona integron-encoded metallo-beta-lactamase (VIM), and imipenemase metallo-beta-lactamase (IMP), were detected and differentiated to verify the results of phenotypic assays regarding carbapenemase production. Conventional polymerase chain reaction (PCR) was used to evaluate the molecular profiles of 69 *Acinetobacter* species isolated in pure culture from blood samples. The DNA from the isolates was extracted using a cell lysis step and boiling method with the InstaGene Matrix (Bio-Rad Laboratories, USA) as per the manufacturer's instructions. The primers utilized in this study were detailed in Table 1.

Results

Clinical Features of Carbapenem-resistant *Acinetobacter* Species

A total of 69/86 *Acinetobacter* species isolates were isolated by conventional biochemical methods as well as by MALDI-TOF method between September 2020 and October 2021 at a tertiary care hospital, King George's Medical University, Lucknow. Out of 69 *Acinetobacter* species, 66 were *A. baumannii*, and three were *Acinetobacter lwoffii*. A total of 61/69 (88.40%) *Acinetobacter* species as carbapenem-resistant isolates were isolated by conventional tests by disk diffusion method and meropenem MICs by VITEK COMPACT 2MS system. We detected carbapenem-resistant genes, as mentioned in the Materials and Methods section, among all *Acinetobacter* species isolates. A total of 20/66 (30.30%) CRAb isolates were detected by conventional polymerase chain reaction (PCR) tests. We detected 20/66 (30.30%) isolates were NDM carbapenemase producers, and other metallo beta-lactamase carbapenem-resistant genes such as IMP and VIM were not found in these isolates. Out of 69, 49 *Acinetobacter* species isolates were negative for metallo beta Lactamase carbapenem-resistant genes like NDM, IMP, and VIM in conventional PCR tests.

A total of 20/61 (32.78%) NDM-detected *A. baumannii* isolates were also positive with m CIM and eCIM phenotypic test. Whereas 39/61 (63.93%) *A. baumannii* isolates were negative for carbapenem-resistant genes in PCR, but all were positive only for the mCIM phenotypic test none were positive for the eCIM phenotypic test.

Table 2: Demographic data and risk factors influencing the development of bloodstream infection in patients infected with NDM-positive *Acinetobacter* species isolates compared to NDM-negative isolates

Variables	*NDM A. baumannii (N = 20)*	*Non NDM A. baumannii (N = 46)*	*p-value*
Gender			
Male	13	31	0.849
Female	7	15	
Age			
20–40	9	20	0.089
>40–60	2	15	
>60	9	11	
History of prior surgery within 3 months	5	22	0.083
Length of hospital stay prior to ICU admission (days), median (minimum-maximum)	16	22	0.015
Exposure to broad-spectrum antibiotics during hospital stay before ICU admission	17	23	0.007
History of prior hospital admission (<6 months)	3	6	0.831
Ventilated	10	21	0.744
Central venous catheter	17	25	0.017
Urinary Foleys catheter	17	32	0.187
Hypertension	10	9	0.012
Diabetes	12	15	0.037
Mortality	15	18	0.007

Table 3: Antibiotic resistance pattern *A. baumannii* of isolates harboring the NDM gene

Name of antibiotics	*NDM A. baumannii (N = 20)*	*% of drug resistance*	*Non NDM A. baumannii (N = 46)*	*% of drug resistance*
Cefepime (30 µg)	18	90	43	88
Ceftazidime (30 µg)	11	55	28	57
Tetracycline	9	45	28	57
Cefoperazone (30 µg)	16	80	35	71.5
Ceftriaxone (30 µg)	19	95	45	91.83
Trimethoprim-sulfamethoxazole (1.25/23.75 µg)	17	85	40	81.6
Piperacillin-tazobactam (10 µg)	18	90	40	81.6
Ciprofloxacin (5 µg)	19	95	42	85.7
Levofloxacin (5 µg)	16	80	47	95.91
Imipenem (10 µg)	20	100	45	91.83
Meropenem (10 µg)	20	100	42	85.7
Tobramycin (10 µg)	18	90	37	75.51
Gentamicin (10 µg)	16	80	37	75.51
Amikacin (30 µg)	18	90	37	75.51
Colistin*	6	12.24	3	6.1

Antimicrobial Susceptibility Patterns

All 20 CRAB isolates confirmed by the genotypic method were resistant to meropenem (100%), imipenem (100%), piperacillin/tazobactam (90%), and isolates had no susceptibility to amikacin (90%), gentamicin (80%), tobramycin (90%), levofloxacin (80%), ciprofloxacin (95%), piperacillin-tazobactam (90), trimethoprim-sulfamethoxazole (85%), cefepime (90%), cefoperazone (80%), and ceftriaxone (95%) whereas the non-susceptibility of NDM-positive *A. baumannii* to the tetracycline and ceftazidime antibiotics was 45 and 55%, respectively. In contrast, NDM-negative *A. baumannii* isolates had lower resistance to ceftazidime, tetracycline, cefoperazone, and aminoglycoside antibiotics of 60.08, 60.08, 76.08, and 80%, respectively. Conversely, all three isolates of *Acinetobacter* lwoffii isolates had no resistance

to all the above antibiotics, and in these isolates, there was no metallo-beta-lactamase gene detected.

Acinetobacter baumannii isolate had the NDM gene and was resistant to most tested antimicrobials except colistin (Tables 2 and 3). However, colistin was observed (6/20, 12.24%) to be resistant in all NDM-positive *A. baumannii isolates*, whereas three isolates out of 46 (6.05%) of NDM-negative *A. baumannii* showed intermediate MIC for colistin.

Risk Factor and Outcome

Both NDM-positive and NDM-negative *Acinetobacter* isolate-positive ICU patient groups exhibited equal demographic data on age and sex, with no discernible correlation. There was a strong positive association ($p < 0.015$) was seen with extended ICU stay (median ICU stay = 7 days), and patients with central venous catheters also had a significant positive correlation (17/20 vs 25/46 $p < 0.017$) for the occurrence of bloodstream infection caused by NDM-positive *Acinetobacter* isolates.

This study also noted that previous exposure to broad-spectrum antimicrobial drugs before hospital admission was very likely significantly associated with acquiring bloodstream infection due to NDM-positive *A. baumannii* isolates (17/20 vs 23/46 $p < 0.007$). Comorbidities, such as hypertension ($p < 0.012$) and diabetes mellitus ($p < 0.037$) had significant risk factors associated with bloodstream infection caused by NDM-positive *A. baumannii* isolates.

A total of 33/69 (55.07%) deaths were observed in the study duration, out of which 15/20 (75%) deaths were observed in patients due to the presence of NDM *A. baumannii isolate* strains, and 18/46 (57.14%) deaths were observed in patients with non-NDM *A. baumannii isolates* with no detectable metallo beta-lactamase gene that is statistically significant ($p < 0.007$).

Discussion

This was an observational hospital study to determine antimicrobial resistance patterns, risk factors, and outcomes for CRAB-associated bacteremia in ICU patients. *Acinetobacter* infections are commonly found in critically ill patients, especially in ICUs. *Acinetobacter* is a significant contributor to hospital-associated bloodstream infections, which can have severe consequences and often result in high morbidity and mortality rates.[11,12] This pathogen demonstrates distinctive mechanisms of resistance to a range of antibiotics, such as carbapenems, and can last in challenging settings on non-living things within the hospital setting. Carbapenem-resistant *Acinetobacter* is becoming more widespread globally.[13] There has been a significant increase in the resistance of *Acinetobacter* isolates to carbapenems in India, with rates ranging from 75 to 88%.[14,15] In this study, we found that most of the *Acinetobacter* isolates (61 out of 69, or 88.4%) were carbapenem non-susceptible.

Another study in India also reported the carbapenem resistance of *A. baumannii isolate* 87.5%.[16,17] Carbapenem resistance signifies a nationwide issue stemming from the indiscriminate and extensive utilization of these antibiotics. The issue of carbapenem resistance has escalated with the revelation of the NDM gene, which confers resistance to carbapenems, the ultimate antibiotics of last resort.[18] It limited the capacity of all β-lactam antibiotic groups to treat infections caused by bacteria with resistance determinants.[19] Our study's most notable finding was the positivity of NDM-positive *A. baumannii* isolates (20/66; 30.30%) in bloodstream infection reported. Among the isolates studied for metallo beta-lactamase producers, 30.30% produced the NDM enzyme; no other metallo beta-lactamase enzyme-producing gene was detected. This shows that carbapenem resistance in *A. baumannii* was not only because of the presence of the NDM gene, but other underlying drug resistance mechanisms like naturally occurring oxacillinases, carbapenemases, and other ambler group genes were also involved. Carbapenem-resistant *A. baumannii* isolates typically resist the majority of current antibiotics such as tetracyclines and ceftazidime because of the combination of OXA enzymes, efflux pumps, and permeability abnormalities. However, this study found resistance to tetracyclines and ceftazidime in 45 and 55% of isolates, which may be due to local factors that may influence variations in resistance mechanisms. All CRAB strains do not exhibit uniform resistance; some may possess OXA enzymes without strong efflux activity, leading to partial sensitivity to agents such as tetracyclines or ceftazidime. Additionally, geographical differences in resistance profiles can affect drug efficacy, particularly in areas where certain antibiotics are less frequently used, reducing the percentage of resistance. The heterogeneity of clinical strains also contributes to varying resistance levels. The present study indicates that some CRAB strains remain susceptible to agents such as tetracyclines or ceftazidime despite carbapenem resistance, linked to efflux pump expression and target site mutations. To understand these atypical susceptibility patterns, further molecular investigations into the resistance mechanisms of isolates are essential, focusing on non-OXA-mediated factors like porin expression and efflux pump variations.[20]

The NDM-1 gene, linked to the Tn125 transposon, was hypothesized to originate from a specific strain of *A. baumannii* in a specific region of the world and be transferred to Enterobacteriaceae.[21]

Tn125 is likely the primary means by which NDM-1 genes are spread among strains of *A. baumannii*. The ISAba125 element is located upstream of the NDM-1 gene and is similarly involved in the horizontal transmission of NDM-1 in *A. baumannii.*[22,23] The study reveals that carbapenem-resistant *Acinetobacter* spp. isolates exhibit a complex interaction of multiple resistance mechanisms, resulting in high phenotypic detection rates.

While *A. baumannii* has OXA-51, a chromosomally encoded enzyme intrinsic to the species, most of the phenotypic resistance to carbapenems is caused by the predominant OXA-51. Ambler-class D beta-lactamases exhibit limited carbapenemase activity; they hydrolyze imipenem and ertapenem more effectively than meropenem.[24,25] The incorporation of an insertion sequence (IS) element, such as ISAbaI and ISAba9, markedly enhances carbapenemase production, leading to clinical carbapenem resistance.[26] In this study, only NDM genes were targeted, so other mechanisms of carbapenem resistance were not well explained, which led to the differences between phenotypic detection methods of metallo beta-lactamases. The extremely low quantity and permeability of porins in its outer membrane and multidrug efflux pumps contribute to *Acinetobacter* spp.'s overall antibiotic resistance. These bacteria can also swiftly pick up extra genetic elements from other bacterial species that confer resistance.[26,27] The present study proved that all (20/20) *Acinetobacter* isolates expressing the NDM were completely resistant to carbapenems and all other tested antibiotics except colistin. The findings of this study are consistent with earlier Indian research that found that *Acinetobacter* isolates with coexisting blaNDM-1 exhibited considerably greater levels of carbapenem resistance than other

blaNDM-1-negative isolates. Studies have observed that most *Acinetobacter* spp. that produce blaNDM-1 remain susceptible to colistin alone. However, when *Acinetobacter* isolates have both blaNDM-1 and blaOXA-23-like genes, the overexpression of these genes leads to heightened resistance to carbapenems and other antibiotics.

The policy of using antimicrobial drugs and the existence of drug-resistant clones in hospitals and ICUs are contributing to the problem of antibiotic resistance in *A. baumannii* isolates. In this study, we observed that most of the drugs were resistant in both NDM *A. baumannii* and non-NDM *A. baumannii* except colistin. Colistin is one of the few therapeutic choices available against CRAB infections, and due to increased use, the colistin resistance rate is progressively increasing globally, posing a healthcare concern. It was found that only 12.24% of *Acinetobacter* isolates showed resistance to colistin in NDM *A. baumannii*. This is consistent with previous studies in India where the resistance rate was low, ranging from 3 to 9.5%.[28] The low resistance rate may be due to colistin being used as a reserve medication for multi-drug resistant pathogens. However, multiple studies have revealed that Pan Drug Resistance *Acinetobacter* has increased clinical importance, possibly because of the increase in the use of colistin; thus, resistance to it is also emerging.[29,30]

With a focus on NDM *A. baumannii* isolate-induced bloodstream infections, this study sought to determine the contributing factors to unfavorable patient outcomes.[31] The results demonstrated that extended ICU stays and longer central venous catheter stays were important risk factors for infection by NDM-positive *Acinetobacter* isolates. A significant association was observed between prior medication use (17/20 vs 23/46; $p = 0.007$) and the acquisition of infections caused by blaNDM-1-positive *Acinetobacter* isolates.[32] In this study, we also reported underlying comorbidities like hypertension and diabetes milletus are significant risk factors for bloodstream infection due to NDM *A. baumannii*. Antibiotic usage in the past has been shown to raise the risk of MDR-*Acinetobacter* bloodstream infection.[33] Furthermore, Nhu et al. and Aneta et al. hypothesized that earlier carbapenem exposure may predispose individuals to later colonization and infection with resistant bacteria.[33] Inappropriate empirical therapy for critical care patients is a significant predictor of mortality in ICUs.

It was found that people who were infected with NDM-positive *Acinetobacter* isolates had significantly higher mortality (75% vs 57.14%, $p = 0.007$). According to other research, the mortality from an *Acinetobacter* bloodstream infection is between 26 and 68%.[34] This high death rate, even with the right treatment, is because of MDR *Acinetobacter* isolates and poor empirical therapy.[35]

Limitations

One limitation of the study was that not all possible mechanisms of carbapenem were done, and one other major limitation was that it was carried out in a single center. In addition, the COVID-19 pandemic had a significant impact on healthcare settings, which likely influenced nosocomial infections like *Acinetobacter* in several ways, but we didn't evaluate the impact of the COVID-19 pandemic on the study population.

Conclusion

Acinetobacter isolates containing the NDM gene, which resists carbapenems, cause most ICU infections. *Acinetobacter* isolates with the NDM gene conferring carbapenem resistance are among the major causes of infection in ICU patients. The most crucial information for guiding appropriate antibiotic therapy is an understanding of *Acinetobacter* resistance patterns, as managing this remains a challenge for doctors. This study emphasizes the risk factors associated with poor outcomes in bloodstream infection of ICU patients. The most important predictors of outcome were NDM-positive *Acinetobacter* isolate infection, longer hospital stay, intensive care unit stay of more than 7 days, history of antimicrobial agent exposure, and inadequate empirical therapy. Reducing incidence and mortality in hospitalized ICU patients requires early detection, infection control, antimicrobial policy, and preventive measures to control strain spread.

Clinical Significance

Bloodstream infections in ICU patients, particularly from NDM-positive *Acinetobacter*, are difficult to treat due to resistance patterns. Prolonged ICU stays, past antibiotic usage, and inadequate early therapy all contribute to poor outcomes. Effective management necessitates early detection, infection control, and customized antimicrobial regimens to limit incidence and death.

Ethical Approval

Ref No: 102nd ECM II B Thesis/P42

Authors' Contributions

A Verma, S Singh, and V Venkatesh: Equally contributed to the conception of the work, design of the work, interpretation of data, and manuscript preparation. V Venkatesh, S Verma, D Himanshu, and A Agarwal: Equally contributed to the revision of the manuscript.

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