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Indian Journal of Microbiology Research

Journal homepage: www.ijmronline.org

Original Research Article

Xpert carba R assay for carbapenem resistant gram-negative bacterial blood culture isolates: An experience at a tertiary care hospital

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Abstract

Background: Carbapenem resistant blood stream infections are a serious threat to provision of effective and affordable healthcare to the patients. It is important to determine the mechanism of the resistance, so that the appropriate treatment can be provided to the patient. The study aims to evaluate the blood stream infections caused by the carbapenem resistant Gram-negative bacteria which were tested by Xpert Carba R assay.
Materials and Methods: Isolates of Gram-negative bacteria from blood culture of the patients, which had been tested by the Xpert Carba R assay, were included in the study after ethical clearance from the institute ethics committee. The clinical details and the laboratory parameters of the patients were collected from the electronic case records. Statistical analysis was done using SPSS version 23.
Results: Forty-nine isolates were included in the study. The assay was negative for 14.3% (7/49) patients. The common genes detected were bla_{NDM}, 67.3% (33/49) and bla_{OXA-48}, 36.7% (18/49). These genes co-occurred in 20.4% (10/49) patients. The crude mortality rate was the least due to the pathogens with the bla_{NDM}, whilst it was highest for the pathogens with bla_{NDM} + bla_{OXA-48}, though not statistically significant.
Conclusions: The Xpert Carba R assay is useful for the carbapenemase gene detection among the Enterobacterales. The bla_{NDM} gene is the commonest gene detected in the study, bla_{NDM} + bla_{OXA-48} co-occurrence is common. The Xpert Carba R assay should be used cautiously for the carbapenem resistant *Acinetobacter* infections, which has higher crude mortality in the study.

Keywords: Xpert carba R assay, blaNDM, blaOXA-48, Carbapenem resistance, Carbapenemase, Blood stream infections.

Received: 30-07-2025; **Accepted:** 07-09-2025; **Available Online**: 20-09-2025

1. Introduction

Antibiotic resistance is an important problem faced by the healthcare facilities. Resistance to drugs like carbapenem are also commonly seen. This is dangerous especially if the carbapenem resistant (CR) bacteria are associated with blood stream infections (BSI). The mechanisms of resistance include production of carbapenemase enzymes which hydrolyse the carbapenems, alteration of the outer membrane porins, overactivity of the efflux pumps or by the alteration of the cell wall transpeptidases.[1]

There are various classes of carbapenemase enzymes which can lead to antibiotic resistance and the treatment varies accordingly. Carbapenemase may be serine carbapenemase, like *Klebsiella pneumoniae* carbapenemase (KPC) which belong to class A, or *Oxacillin hydrolyzing* (OXA) which belong to class D; class B are metallo-beta-lactamases and include 'active on imipenem' (IMP), Verona integron encoded metallo-β lactamase (VIM), and New Delhi metallo- β lactamase (NDM).[1,2]

Xpert Carba-R assay has a high diagnostic accuracy in detecting the carbapenemase producing organisms. It detects five beta lactamase (*bla*) carbapenemase genes i.e., bla_{KPC}, bla_{NDM}, bla_{IMP-1}, bla_{VIM} and bla_{OXA-48}.[3,4] In this study we try to determine the epidemiology of the carbapenemase genes

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https://doi.org/10.18231/j.ijmr.12638.1934849221

among the patients with blood stream infections and associated clinical outcomes.

2. Materials and Methods

The study was conducted after receiving the ethical approval from the Institute Ethics committee. In this observational study the blood isolates that were tested for the carbapenemase genes by Xpert Carba R assay (Cepheid, Sunnyvale, CA) in the tertiary care hospital, were included. The pathogens were tested by Xpert Carba R assay based on the request of the clinical team. The blood culture of the patients had been done by BD BACTEC (Becton Dickinson, East Rutherford, NJ, USA) blood culture systems. The identification of the isolates done by conventional methods and/or by BD Phoenix system (Becton Dickinson, East Rutherford, NJ, USA) and antibiotic susceptibility of the isolates was done by Kirby Bauer susceptibility test, according CLSI document M100, 29th edition, 2019 (Clinical and Laboratory Standards Institute, Wayne, PA). Antibiotic discs, imipenem 10µg, meropenem 10µg, HiMedia Laboratories Pvt. Ltd, Mumbai, India were used. The pathogens were considered carbapenem resistant, if they were resistant either to imipenem or meropenem. The tests conducted from September 2019 to June 2023, were included in the study

Statistical analysis was done using the SPSS version 23. The demographic details, course in the hospital, antibiotic treatment and the outcome was collected from the electronic records. Microbiological source was determined based on the whether the pathogen isolated in the blood was also isolated in culture of other samples sent during the time of hospital stay of the patient. The continuous variables were tested for normality of distribution and then expressed in terms of median or mean. The categorical variables have been expressed in terms of numbers and percentages. The association between the various variables and the bla_{NDM} and bla_{OXA-48} gene, or the different pathogens was done either by independent t test, Mann Whitney U test, Chi square test or Fishers exact test, based on the type of the variable tested.

3. Results

Forty-nine Carbapenem resistant (CR) Gram Negative bacterial (GNB) isolates from blood had been tested by Xpert Carba R assay, based on the request by the treating physicians. The median age of the patients, whose isolates were tested, was 56 years, 28 (57.1%) of the patients were males and the patients had a mean length of hospital stay for 21.78±11.83 days. The most common primary source detected in the study was urine 13/49 (26.5%), and lungs 8/49 (16.3%). In 25/49 (51%) of the cases, the microbiological source could not be determined.

Among the patients whose isolates were tested, 35/49 (71.4%) had undergone ICU admission, 25/49 (51%) had undergone mechanical ventilation. The most common genes detected were bla_{NDM}, 33/49 (67.3%), bla_{OXA-48}, 18/49 (36.7%), among these, both bla_{NDM} and bla_{OXA-48} were detected in 10 isolates. Polymyxins were administered to 30/49 (61.22%) of the patients, during hospitalization. Twenty-two (44.9%) of the patients succumbed to the blood stream infection, 23/49 (46.9%) were discharged and 4/49 (8.2%) of patients left against medical advice.

The most common organisms isolated were *Klebsiella pneumoniae* (*Kp*) 23/49 (46.9%) and *Escherichia coli* (*Ec*) 11/49 (22.45%), *Acinetobacter* species (*Ac*) and *Enterobacter* species (*En*), each 7/49 (14.28%).

The **Figure 1**, shows the distribution of the pathogens and the resistance genes shows the distribution of the different pathogens, and the resistance genes tested in the study.

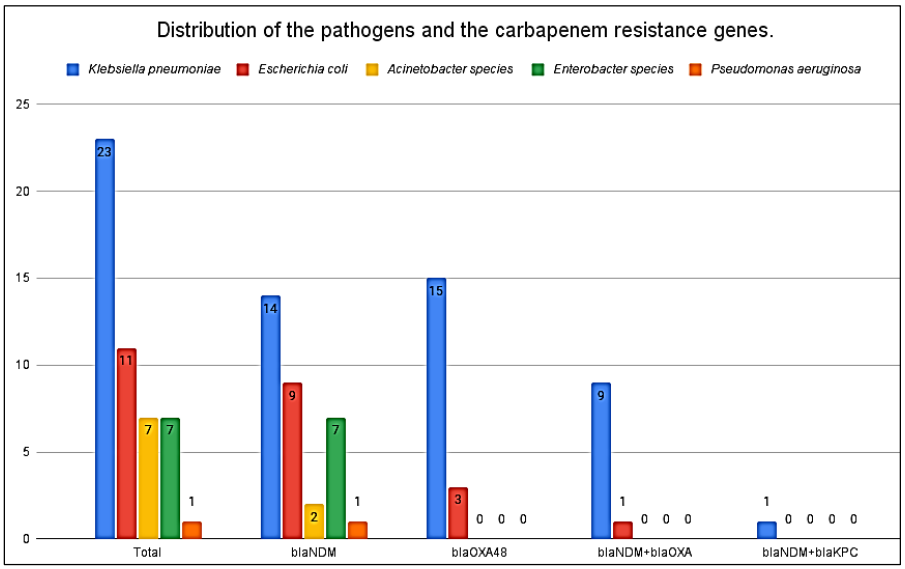

Figure 1: Distribution of the pathogens and the carbapenem resistance genes

As shown in the **Table 1**, *bla*$_{NDM}$ genes were detected in 33(67.3%) of the isolates. Fourteen (42.4%) were in CR*Kp*, 9 (27.3%) in CR*Ec*, 7 (21.2%) in CR*En* and 2 (6.1%) in CR*Ac* and 1 (3.0%) in the CR *Pseudomonas aeruginosa*. All cause in-hospital mortality was seen in 12 (36.4%) of the patients with *bla*$_{NDM}$ positive isolate.

The *bla*$_{OXA-48}$ gene was detected in 18 (36.7%) isolates. Fifteen (83.3%) of the genes were isolated *in* CR*Kp* and 3 (16.7%) of the genes were detected in CR*Ec*. The crude in hospital mortality among the patients with *bla*$_{OXA-48}$ gene was 66.7%.

Ten (20.4%) of the isolates tested had both *bla*$_{NDM}$ and *bla*$_{OXA-48}$ genes. Nine (90%) of these patients had undergone ICU admission and mechanical ventilation. Nine (90%) of the genes were isolated in CR*Kp* isolates and one (10%) of the genes was isolated in CR*Ec*. All the patients with both the genes in the pathogens were treated with polymyxin B. Seven (70%) of these patients had an all cause in hospital mortality.

Table 1: Characteristics of the different resistance genes

	Number N=49	***bla*$_{NDM}$ detected 33 (67.3%)**	**P_1 value**	***bla*$_{OXA-48}$ detected 18 (36.7%)**	**P_2 value**	***bla*$_{NDM}$ + *bla*$_{OXA-48}$ detected 10 (20.4%)**	**P_3 value**
Median Age in years	56 (42-65.50)	48 (31.5-62.50)	0.074*	56 (45-66)	0.779*	46.5 (39.5-60.25)	0.223*
Male	28 (57.1%)	19 (57.6%)	0.930†	8 (44.4%)	0.171†	3 (30.0%)	0.076‡
Mean Length of hospital stay in days	21.78 ±11.83	21.61±10.76	0.887§	21.44±12.49	0.883§	19.80±10.12	0.559§
Source			0.375‡		0.374‡		0.407‡
Urine	13 (26.5%)	10 (30.3%)		5 (27.8%)		3 (30.0%)	
Lungs	8 (16.3%)	4 (12.1%)		5 (27.8%)		3 (30.0%)	
Central line	3 (6.1%)	3 (9.1%)		1 (5.6%)		1 (10.0%)	
Unknown	25 (51.0%)	16 (48.5%)		7 (38.9%)		3 (30%)	
ICU admission	35 (71.4%)	21 (63.6%)	0.104‡	15 (83.3%)	0.160†	9 (90.0%)	0.244‡
Mechanical ventilation	25 (51.0%)	16 (48.5%)	0.610†	14 (77.8%)	**0.004**†	9 (90.0%)	**0.011**‡
Malignancy	5 (10.2%)	4 (12.1%)	1.000‡	0	0.143‡	0	0.569‡
Central line	20 (40.8%)	14 (42.4%)	0.742†	7 (38.9%)	0.834†	4 (40.0%)	1.000‡
Haemodialysis	10 (20.4%)	5 (15.2%)	0.261‡	6 (33.3%)	0.141‡	4 (40.0%)	0.181‡
Organisms			**0.038**†		**0.002**†		**0.046**†
Klebsiella pneumoniae	23 (46.9%)	14 (42.4%)		**15 (83.3%)**		**9 (90.0%)**	
Escherichia coli	11(22.4%)	9 (27.3%)		3 (16.7%)		1 (10.0%)	
Acinetobacter species	7 (14.3%)	**2 (6.1%)**		**0**		0	
Enterobacter species	7 (14.3%)	**7 (21.2%)**		**0**		**0**	
Pseudomonas aeruginosa	1 (2.0%)	1 (3.0%)		0		0	
Antibiotics received by patients							
Tigecycline	5 (10.2%)	4 (12.1%)	1.000‡	4 (22.2%)	0.054‡	3 (30%)	0.051‡
Polymyxins	29 (59.2%)	23 (69.7%)	**0.032**†	13 (72.2%)	0.157†	10 (100%)	**0.003**‡
Outcome			0.090‡		0.070‡		0.119‡
Death	22 (44.9%)	12 (36.4%)		**12 (66.7%)**		7 (70.0%)	
Discharge	23 (46.9%)	19 (57.6%)		5 (27.8%)		2 (20.2%)	
DAMA	4 (8.2%)	2 (6.1%)		1 (5.6%)		1 (10.0%)	

P value<0.05 was considered significant

Abbreviations: ICU, Intensive care unit, DAMA, Discharge against medical advice.

P_1 value – comparison between *bla*$_{NDM}$ and non *bla*$_{NDM}$ isolates

P_2 value – comparison between *bla*$_{OXA-48}$ and non *bla*$_{OXA-48}$ isolates

P_3 value – comparison between *bla*$_{NDM}$ + *bla*$_{OXA-48}$ and non *bla*$_{NDM}$ + *bla*$_{OXA-48}$ isolates

*- Mann Whitney U test, † - Chi square test, ‡ - Fishers Exact test, § - Independent t test

The **Table 2** shows that among the 7 isolates of CR*Ac*, carbapenemase- bla_{NDM} genes by Carba R were detected only in 2 (28.6%) of the isolates. None of the carbapenemase genes were detected among 5 of the CR*Ac* isolates by the Carba R test. Six (85.7%) of the patients with CR*Ac* expired in the hospital.

The **Table 3** shows the baseline characteristics of the patients with the different common pathogens isolated from the blood culture samples, when compared to the patients without those pathogens among the study population.

The Xpert Carba R assay was negative in 2/23 (8.7%) CR*Kp* isolates in the study. bla_{OXA-48} was the most common gene isolated among the isolates of CR*Kp*, found in 15/23 (65.2%), bla_{NDM}, 14/23 (60.9%) and in bla_{KPC} in 1/23 (4.3%) isolates. The bla_{KPC} gene was found along with bla_{NDM} gene in one of the isolates. Similarly, 9/23 (39.1%) of the CR*Kp* isolates had both bla_{NDM} and bla_{OXA-48} genes. Twelve (52.2%) of the patients with CR*Kp* in blood had all cause in hospital mortality.

Among the 11 isolates of CR*Ec*, urine was the source for 6 isolates. Carbapenemase were detected in all the isolates of CR*Ec* by the Xpert Carba R assay. bla_{NDM} gene was detected in 9 (81.8%) of the CR*Ec* isolates and bla_{OXA-48} was detected in 3 (27.3%) isolates. bla_{NDM} and bla_{OXA-48} genes were both present in one of the isolates. Crude mortality rate was 27.3% (3/11) for the patients with CR*Ec* infections.

Table 2: Characteristics of the patients with CR*Ac* BSIs in the study

	Number n=49	**CR*Ac* 7/49 (14.29%)**	**Other pathogens 58.7% (42/49)**	***P*3 value**
Median Age in years	56 (42-65.50)	56 (21-64.5)		0.665*
Male	28 (57.1%)	3 (42.9%)	25 (59.5%)	0.443‡
Mean Length of hospital stay in days	21.78 ±11.83	18.14 ±14.43		0.386§
Source				0.188‡
Urine	13 (26.5%)	0	13 (31.0%)	
Lungs	8 (16.3%)	1 (16.7%)	7 (16.7%)	
Central line	3 (6.1%)	0	3 (7.1%)	
Unknown	25 (51.0%)	6 (85.7%)	19 (45.2%)	
ICU admission	35 (71.4%)	7 (100%)	28 (66.7%)	0.170‡
Mechanical ventilation	25 (51.0%)	4 (57.1%)	21 (50%)	1.000‡
Malignancy	5 (10.2%)	1 (14.3%)	4 (9.5%)	0.554‡
Central line	20 (40.8%)	4 (57.1%)	16 (57.1%)	0.422‡
Haemodialysis	10 (20.4%)	2 (28.6%)	8 (19.0%)	0.620‡
Xpert Carba R assay				
Positive	42 (85.7%)	2 (28.6%)	40 (95.2%)	**0.000**‡
Negative	7 (14.3%)	5 (71.4%)	2 (4.8%)	
Resistance genes detected				
bla_{NDM}	33 (67.3%)	2 (28.6%)	31 (73.8%)	**0.030**‡
bla_{KPC}	1 (2.0%)	0	1 (2.4%)	1.000‡
bla_{OXA-48}	18 (36.7%)	0	18 (42.9%)	**0.038**‡
bla_{NDM} +bla_{OXA-48}	10 (20.4%)	0	10 (23.8%)	0.319‡
Antibiotics prescription pattern				
Tigecycline	5 (10.2%)	0	5 (11.9%)	1.000‡
Polymyxins	29 (59.2%)	3 (42.9%)	26 (61.9%)	0.422‡
Outcome				**0.020**‡
Death	22 (44.9%)	6 (85.7%)	16 (38.1%)	
Discharge	23 (46.9%)	0	23 (54.8%)	
DAMA	4 (8.2%)	1 (14.3%)	3 (7.1%)	

P value<0.05 was considered significant

*- Mann Whitney U test, † - Chi square test, ‡ - Fishers Exact test, § - Independent t test

Abbreviations: CR*Ac*, Carbapenem resistant *Acinetobacter* species, ICU, Intensive care unit, DAMA, Discharge against medical advice.

Table 3: Characteristics of the patients with different blood pathogens

	Number	CR*Kp* 23/49 (46.9%)	P_1 value	CR*Ec* 11/49 (22.45%)	P_2 value	CR*Ac* 7/49 (14.29%)	P_3 value	*CREn* 7/49 (14.29%)	P_4 value
Median Age in years	56 (42-65.50)	57 (46-64.50)	0.575*	62 (52.5-70)	0.204*	56 (21-64.5)	0.665*	42 (1-48)	**0.045***
Male	28 (57.1%)	14 (53.8%)	0.620†	6 (54.5%)	1.000‡	3 (42.9%)	0.443‡	4 (57.1%)	1.000‡
Mean Length of hospital stay in days	21.78 ±11.83	21.30±11.42	0.796§	19.82±12.5	0.539§	18.14 ±14.43	0.386§	28 ± 8.43	0.134§
Source			0.090‡		**0.047**‡		0.188‡		0.056‡
Urine	13 (26.5%)	5 (21.7%)		6 (54.5%)		0		2 (28.6%)	
Lungs	8 (16.3%)	7 (30.4%)		0		1 (16.7%)		0	
Central line	3 (6.1%)	1 (4.3%)		0		0		2 (28.6%)	
Unknown	25 (51.0%)	10 (43.5%)		5 (45.5%)		6 (85.7%)		3 (42.9%)	
ICU admission	35 (71.4%)	17 (73.9%)	0.717†	7 (63.6%)	0.706‡	7 (100%)	0.170‡	4 (57.1%)	0.392‡
Mechanical ventilation	25 (51.0%)	15 (65.2%)	0.062†	3 (27.3%)	0.074†	4 (57.1%)	1.000‡	3 (42.9%)	0.702‡
Malignancy	5 (10.2%)	1 (4.3%)	0.353‡	2 (18.2%)	0.311†	1 (14.3%)	0.554‡	1 (14.3%)	0.554‡
Central line	20 (40.8%)	10 (43.5%)	0.721†	2 (18.2%)	0.162‡	4 (57.1%)	0.422‡	4 (57.1%)	0.422‡
Haemodialysis	10 (20.4%)	7 (30.4%)	0.157‡	1 (9.1%)	0.419‡	2 (28.6%)	0.620‡	0	0.319‡
Xpert Carba R test									
Positive	42 (85.7%)	21 (91.3%)	0.424‡	11 (100%)	0.325‡	2 (28.6%)	0.000‡	7 (100%)	0.573‡
Negative	7 (14.3%)	2 (8.7%)		0		5 (71.4%)		0	
Resistance genes detected									
bla$_{NDM}$	33 (67.3%)	14 (60.9%)	0.363†	9 (81.8%)	0.300‡	2 (28.6%)	**0.030‡**	7 (100%)	0.080‡
bla$_{KPC}$	1 (2.0%)	1 (4.3%)	0.469‡	0	1.000f	0	1.000‡	0	1.000‡
bla$_{OXA-48}$	18 (36.7%)	15 (65.2%)	**0.000†**	3 (27.3%)	0.724‡	0	**0.038‡**	0	**0.038‡**
bla$_{NDM}$ + *bla*$_{OXA-48}$	10 (20.4%)	9 (39.1%)	**0.003‡**	1 (9.1%)	0.419‡	0	0.319‡	0	0.319‡
Antibiotics prescription pattern									
Tigecycline	5 (10.2%)	4 (17.4%)	0.173‡	1 (9.1%)	1.000‡	0	1.000‡	0	1.000‡
Polymyxins	29 (59.2%)	13 (56.5%)	0.721†	7 (63.6%)	1.000‡	3 (42.9%)	0.422‡	6 (85.7%)	0.216‡
Outcome			0.633‡		0.509‡		**0.020‡**		0.095‡
Death	22 (44.9%)	12 (52.2%)		3 (27.3%)		6 (85.7%)		1 (14.3%)	
Discharge	23 (46.9%)	9 (39.1%)		7 (63.6%)		0		6 (85.7%)	
DAMA	4 (8.2%)	2 (8.7%)		1 (9.1%)		1 (14.3%)		0	

P value<0.05 was considered significant

*- Mann Whitney U test, † - Chi square test, ‡ - Fishers Exact test, § - Independent t test

P_1 value – comparison between CR*Kp* and non CR*Kp* isolates

P_2 value – comparison between CR*Ec* and non CR*Ec* isolates

P_3 value – comparison between CR*Ac* and non CR*Ac* isolates

P_2 value – comparison between CR*En* and non CR*En* isolates

Abbreviations: CR*Kp*, Carbapenem resistant *Klebsiella pneumoniae*, CR*Ec*, Carbapenem resistant *Escherichia coli*, CR*Ac*, Carbapenem resistant *Acinetobacter* species, CR*En*, Carbapenem resistant *Enterobacter* species, ICU, Intensive care unit, DAMA, Discharge against medical advice.

Seven of the patients had CR*En* isolated from the blood. Source of the two each (28.6%) of the isolates were urine and central line. All the CR*En* isolates tested were positive for *bla*$_{NDM}$ gene. In hospital mortality was seen in one (14.3%) of these patients.

4. Discussion

Carbapenem resistant infections especially in the blood is a very important problem faced by healthcare systems in the effective treatment of the patients. The response to the different treatments of these infections may vary depending on the mechanism of resistance. Hence it is important to identify the resistance mechanisms underlying the

carbapenem resistance especially in serious infections like the bloodstream infections.

For the 49 carbapenem resistant GNBSIs included in the study, the median age was 56 years, males accounted for 57% of the cases (28/49). The mean length of stay was 21.78 ±11.83 days. The most common identified source of infection was urine (13/49, 26.5%). Thirty-five (71.4%) of the patients underwent ICU admission during the hospital stay and 25/49 (51.0%) of the patients had undergone mechanical ventilation. Five (10.2%) of the patients had malignancy and 40.8% (20/49) patients had central venous catheter inserted. Ten (20.4%) patients were undergoing haemodialysis.

The most common pathogens which were tested were CR*Kp* (46.9%, 23/49), followed by CR*Ec* (11/49, 22.4%), CR*Ac* (7/49, 14.3%), CR*En* (7/49, 14.3%) and *Pseudomonas aeruginosa* (1/49, 2.0%). This is consistent with a study which showed that most common Carbapenem resistant GNBSI was CR*Kp*, and CR*Ec* was the overall most common GNB to cause BSI. The third most common pathogen to cause BSI was CR*Ac*.[5]

In the present study, the carbapenemase genes detected by the Xpert Carba R assay were bla_{NDM}, 67.3% (33/49), $bla_{\text{OXA-48}}$, 36.7% (18/49) and bla_{KPC}, 2.0% (1/49). Co-occurrence of bla_{NDM} and $bla_{\text{OXA-48}}$ genes was detected in 20.4% (10/49) isolates. The bla_{KPC} was also detected in combination with bla_{NDM}. Similar findings have been reported by Nayak et al, in a study conducted in Bhubhaneshwar, Orissa.[6] However in another study conducted in Chennai, by Gopalakrishnan et al., it was found that $bla_{\text{OXA-48}}$ was the most common carbapenemase gene, detected in 65.51% of the isolates, followed by bla_{NDM} (50%). $bla_{\text{OXA-48}}$ + bla_{NDM} co-occurrence was detected in 15.51% of the isolates tested from blood cultures by Xpert Carba R assay.[7] Studies in Pondicherry[8] and Mumbai,[9] on the isolates from ICU have identified OXA-48 like to be the most common carbapenemase genes, whereas co-occurrence of bla_{NDM} + $bla_{\text{OXA-48}}$ like was the most common in a study in Pune.[10] Worldwide, different studies have reported bla_{NDM} to be common in Iran,[11] Nigeria[12] and Mexico,[13] $bla_{\text{OXA-48}}$ like in Saudi Arabia[14] and Turkey,[15] bla_{KPC} in United States,[16] China[17] and Taiwan.[18]

The bla_{NDM} gene (67.3%, 33/49) was the most common carbapenemase gene detected in our study population. All the CR*En* strains tested in the study were positive for bla_{NDM}. The crude mortality rate for the isolates with bla_{NDM} gene was 36.4% (12/33).

The $bla_{\text{OXA-48}}$ gene was the second most common (36.7%, 18/49) carbapenemase gene detected in the study. The isolates with $bla_{\text{OXA-48}}$ genes have a significant association with mechanical ventilation (14/18, 77.8%, *P*-0.004). CR*Kp* was significantly associated with positive $bla_{\text{OXA-48}}$ test accounting for 83.3% (15/18) of the strains positive for $bla_{\text{OXA-48}}$ gene. On the other hand, CR*En* and CR*Ac* were significantly associated with negative test for $bla_{\text{OXA-48}}$ gene, as all the strains tested were negative for the gene. This is consistent with many other studies worldwide, which did not detect $bla_{\text{OXA-48}}$ like genes in CR*Ac*.[1-21] The crude mortality rate among the patients with the isolates positive for $bla_{\text{OXA-48}}$ was 66.7% (12/18).

The co-occurrence of the bla_{NDM} and $bla_{\text{OXA-48}}$ was seen in 20.4% (10/49) of the study isolates. There was significantly high association of CR*Kp* with bla_{NDM} + $bla_{\text{OXA-48}}$ and it accounted for 90% (9/10) of the strains positive for both these genes. Similar trends of co-occurrence of these 2 genes have been demonstrated in various studies across India and the world.[6,7,11] Solgi et al demonstrated that conjugative plasmids carrying bla_{NDM} + $bla_{\text{OXA-48}}$ spread among the Enterobacterales in the hospitals.[11] The crude mortality rate of the patients with isolates positive for both these genes was 70.0% (7/10).

It is interesting to note that the crude mortality rate in the study was (36.4%, 12/33) for the patients with isolates with bla_{NDM}, 66.7% (12/18) for $bla_{\text{OXA-48}}$ and 70% (7/10) for bla_{NDM} + $bla_{\text{OXA-48}}$. Though this finding was not statistically significant and will require further studies to confirm the association.

A very interesting finding of the study is that 71.4% of CR*Ac* had a significant association with negative Xpert Carba R assay when compared to other pathogens. (*P* - 0.000). This has been demonstrated in another Indian study by Nayak et al, where 56.7% of the CR*Ac* were negative for all the 5 genes by Xpert CarbaR test.[6] In many recent studies, worldwide, it has been demonstrated that most CR*Ac* isolates, do not harbour $bla_{\text{OXA-48}}$, bla_{NDM}, rather they carry $bla_{\text{OXA-51}}$, $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-24}}$ genes.[1-22] Hence Xpert Carba R assay is not a reliable test for the detection of the carbapenem resistance genes for CR*Ac* genes. This is unfortunate as the patients with CR*Ac* BSI in the study had a significantly higher mortality rate (85.7% *P*-0.020) when compared to other pathogens. This may hinder the appropriate selection of antibiotics. The drug recommended by Infectious Disease IDSA for CR*Ac* infections is a regimen consisting of high dose sulbactam and should be administered immediately to these patients.[23]

Tigecycline was prescribed to 10.2% (5/49) of the study patients and polymyxins were prescribed to 46.9% (23/49) patients. It is seen in the study that the polymyxins were prescribed significantly more to the patients with isolates that tested positive for bla_{NDM} (69.7%, 23/33, p-0.032) or bla_{NDM} + $bla_{\text{OXA-48}}$ (100%, 10/10, p-0.003). Ceftazidime avibactam with aztreonam, was prescribed for only 2 of the patients in the present study. There are studies with contradictory findings on the usefulness of this antibiotic.[24,25] Further studies with larger sample size are required to demonstrate the efficacy of the drug beyond doubt. Also, the infection control and antibiotic stewardship practices in the hospitals need to be strengthened, as it can be noted that these

infections worldwide occur in critically ill patients with long hospital stays and therapeutic procedures.[5,8,14,1,26,27]

The present study has limitations of it being a retrospective study from a single centre. Also, the pathogens were tested by Xpert Carba R assay based on the discretion of the clinicians and affordability of the patients. The sample size of the study is small, and the findings need to be confirmed by larger prospective studies. Nevertheless, this is one of the first study in India which studies the molecular epidemiology and clinical outcomes of CR GNBSIs and provides important clues to the management and prognosis of these infections.

5. Conclusions

The isolates tested in our study was CR*Kp* (23/49), CR*Ec* (11/49), CR*Ac* (7/49), CR*En* (7/49) and CR *Pseudomonas aeruginosa* (1/49). We found that the most common CR gene was bla_{NDM} (67.3%) followed by bla_{OXA-48} (36.7%) among the blood pathogens. Co-occurrence of bla_{NDM}+ bla_{OXA-48} occurred in 20.4% of the cases. Seven (14.3%) of the pathogens tested negative for Xpert Carba R assay. Crude mortality rate was least for the patients with bla_{NDM} (36.4%), highest for the patients with pathogens with co-occurrence of bla_{NDM}+ bla_{OXA-48} (70%), though this was not statistically significant. The crude mortality rate was highest for CR*Ac* BSIs (6/7, 85.7%). CR*Ac* isolates were associated significantly with negative Xpert Carba R assay. Hence the test has least usefulness for CR*Ac* infections and the results for the same should be interpreted with caution.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflicts of interest.

8. Ethical Approval

This study was approved by institute ethical approval committee with ref. no. FMIEC/CCM/622/2024.

9. Author Contributions

All the authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data or drafting the work and substantively revising it.

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Cite this article: Bhat PN, Prabhu K, Shetty AK, Nayak SG. Xpert carba R assay for carbapenem resistant gram-negative bacterial blood culture isolates: An experience at a tertiary care hospital. *Indian J Microbiol Res*. 2025;12(3):381–388.