How to Cite:
Singh, H., Brar, P. K. S., Kumar, V., Bhardwaj, S., & Dhawan, G. (2022). Carbepenam resistance prevalence in north India: A retrospective analysis. *International Journal of Health Sciences*, *6*(S2), 10851–10857. https://doi.org/10.53730/ijhs.v6nS2.7904

Carbepenam resistance prevalence in north India: A retrospective analysis

Dr Harpreet Singh
Assistant professor, Dept of Anaethesiology, Saraswati medical college, Unnao, U.P.
Email: dr.harpreet85@yahoo.com

Dr Phool Kanwar Singh Brar
M.B.B.S, M.D, IDCCM, I.C.U. Director, Dept of Critical Care, Park Healing Touch Hospital, Ambala
Email: 1973studbrar@gmail.com

Dr. Vikas Kumar
Associate professor, Department of anesthesia, Adesh medical college and hospital, Kurukshetra Haryana.
Corresponding author email: 001vkv@gmail.com

Dr Shital Bhardwaj
Consultant Gynaecologist, Pristyn care, Chandigarh
Email: dr.harpreet1@yahoo.com

Dr. Gulshan Dhawan
Associate Professor, Dept of Anaethesiology, Adesh Medical College and Hospital, Kurukshetra, Haryana, India
Email: gulshan.dhawan@gmail.com

***Abstract*---**Background: We investigated the clinical consequences of healthcare-associated bacteremia in light of rising antimicrobial resistance and limited therapy choices for carbapenem-resistant bacteremia. Methods: Between March 2020 and March 2022, a retrospective observational study of carbapenem-resistant Gram-negative bacteremia was conducted at a tertiary care hospital in North India. Results: Patients in our study spent an average of 11.76 days in the intensive care unit (ICU), with a mean time to bacteremia of 6.4 days following admission. Klebsiella pneumoniae was the most prevalent pathogen (44 percent). Patients receiving combination treatment had a reduced death rate (44.8%) than those receiving colistin monotherapy (66.6%) (P = 0.35). Conclusion: Carbapenem resistant bacteremia is a late-onset illness that affects patients who

have been exposed to antibiotics in the ICU and has a 60 percent mortality rate after 30 days.

***Keywords*---**carbepenam resistance prevalence, bacteremia, Indian intensive care.

Introduction

Enterobacteriaceae (CRE) (including E. coli [CREC] and Klebsiella pneumoniae [CRKP]), Pseudomonas aeruginosa (CRPA), and Acinetobacter baumannii (CRAB) are key emerging sources of nosocomial blood stream infections and carry high mortality. The US Centers for Disease Control and Prevention (CDC) recently designated CRE as a "urgent threat," while the Antimicrobial Availability Task Force of the Infectious Diseases Society of America identified CRPA and CRAB as being of particular concern,[1,2] due to rising antimicrobial resistance among these isolates and dwindling therapeutic options. [3] Carbapenem resistance is seen in up to 12-15 percent of Enterobacteriaceae and 40-60 percent of A. baumanii and P. aeruginosa in single-center investigations in India. [4,5]

Methods

We identified all blood culture results that had shown a growth of carbapenem-resistant GNB during the study period, which took place at a 600-bed tertiary care hospital in North India between May 2019 and May 2021. The medical records of these patients were then examined. The analysis only looked at the first bacteremic event for each patient. The BacT/ALERT (Biomerieux) culture system was used to grow blood, and the VITEK-GNI card was used to identify species (Biomerieux). Antibiotic susceptibility was determined using revised Clinical and Laboratory Standards Institute performance standards and disc diffusion interpretative criteria. [6] Gram-negative bacteremia was defined as the isolation of Gram-negative bacteria in blood culture specimens from at least two bottles of two different culture sets, with clinical characteristics consistent with systemic inflammatory response syndrome.

Demographic and clinical data were examined in medical records. Acute Physiology and Chronic Health Evaluation (APACHE) II score on the day of bacteremia onset, presumed source of infection, and presence of arterial and venous central catheters or hemodialysis catheters were among the clinical parameters examined. The source of bacteremia was determined based on clinical and microbiologic evaluations utilising the CDC's infection criteria. [7] Diabetes, recent surgery, organ transplant, and immunosuppression were all noted as risk factors. Prior antibiotic use, colistin dose, and the need for renal replacement therapy (RRT) after colistin treatment began were also recorded. The survival rate was measured 30 days following the commencement of bacteremia.

Results

The records of 50 patients with CREC, CRKP, CRAB, and CRPA-related bacteremia were found and studied. The average age of the patients was 52.3 years, with 32

(64%) of them being male. Diabetes mellitus was the most frequent co-morbid condition (30 percent), followed by chronic renal disease (22 percent). Five patients (10%) had undergone a liver transplant, while three had undergone other procedures. The average length of stay in the hospital was 24.68 days, with an average of 11.76 days in the intensive care unit (ICU). Bacteremia was diagnosed on average 6.4 days after admission. Antibiotics had already been given to 96 percent of the 50 patients, including beta-lactam/beta-lactamase inhibitors (32 percent) and carbapenems (14 percent) (40 percent)

Table 1 Clinical data

Characteristics	Value in numbers
Age in years (mean±SD)	52.3±15.4
Male sex	32
APACHE II score at onset of bacteraemia (mean±SD)	19.64±3.8
Comorbid condition (*n*=patients)	
Diabetes mellitus	15
CKD	11
Liver disease	5
Malignancy	3
Solid organ transplantation	5
Steroid use	7
Postoperative state	3
Total duration of hospitalization (mean days)	24.68
ICU days (mean)	11.76
Septic shock at presentation (*n*=patients)	19
Time to onset of bacteraemia after admission (mean days)	6.4
Prior receipt of antibiotics (*n*=patients)	
BL+BLI	16
Carbapenems	20
Glycopeptides	15
No antibiotics	2
Total daily dose of colistin (mean)	5.18 million units
Mean loading dose of colistin	5.14 million units
eGFR at initiation of colistin (mean)	52.48 ml/min
Need of RRT after colistin initiation (*n*=patients)	6

SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; CKD: Chronic kidney disease; ICU: Intensive care unit; BL: Beta lactam; BLI: Beta-lactamase inhibitors; eGFR: Estimated glomerular filtration rate; RRT: Renal replacement therapy

At the commencement of bacteremia, the mean (standard deviation [SD]) APACHE II score was 19.64 3.8. Septic shock complicated bacteremia in 38 percent of individuals (n = 19). The cause of 14 cases of bacteremia (28%) was ventilator-associated pneumonia (VAP), 12 episodes (24%) was central line related bloodstream infections (CLABSI), 10 episodes (20%) was intra-abdominal infections (IAI), and 9 episodes (18%) was urinary tract infections. In our investigation, the most common causal organism was CRKP (44%) followed by

CREC (26%), with CRAB and CRPA being isolated in 20% and 10% of patients, respectively.

Table 2
Observed outcome of patients

Source of infection	Number of episodes	Outcome of patients (*n*=patients)	
		Survivors	Nonsurvivors*
CLABSI	12	4	8
Pneumonia	14	5	9
Abdomen	10	4	6
Urine	9	4	5
Unknown	5	3	2
Microrganism	Number of isolates		
Escherichia coli	13	8	5
Klebsiella pneumonia	22	7	15
Acinetobacter baumannii	10	3	7
Pseudomonas aeruginosa	5	2	3

*Includes patients who died and were discharged against medical advice.
CLABSI: Central line related blood stream infections

All patients received a loading dose of colistin of 5.14 million units intravenously, followed by a total daily dose of 5.18 million units. At the start of colistin therapy, the mean creatinine clearance (calculated estimated glomerular filtration rate [eGFR]) was 52.48 ml/min. Following the commencement of colistin for worsening renal function, six patients (12%) required RRT; all returned to normal renal function.

In our study, overall survival at 30 days was 40%, with CLABSI patients having the lowest survival rate (33.3%) and VAP, IAI, and urosepsis patients having survival rates of 35.7 percent, 40 percent, and 44.4 percent, respectively. Overall, CRAB and CRKP bacteraemia had the lowest 30-day survival rates (30 percent and 31.8 percent, respectively), while CRPA and CREC bacteraemia had 40 percent and 61.5 percent, respectively.Patients receiving combination therapy had a reduced mortality rate (44.8%) than those receiving colistin monotherapy (66.6%), albeit this was not statistically significant (P = 0.35).

Table 3
Combination Vs Monotherapy: Treatment outcome

	Combination treatment[$]	Colistin monotherapy
Number of patients continued or completed treatment	29	12
Died (*n*=patients) (%)	13 (44.8)	8 (66.6)
P[#] (using Chi-square test)	0.35	

[$]Combination used were: Colistin+meropenem/tigecycline for CRE; Colistin+meropenem/tigecycline/sulbactam for CRAB isolates; Colistin+meropenem for CRPA. [#]Two-tailed *P* value between combination versus monotherapy groups. CRE: Carbapenem resistant *Enterobacteriaceae*; CRAB: Carbapenem resistant *Acinetobacter baumanni*; CRPA: Carbapenem resistant *Pseudomonas aeruginosa*

Discussion

In India, carbapenem resistance in Gram-negative bacteria is becoming more common in healthcare-associated diseases. Previous investigations from other countries have indicated that bacteremic episodes caused by these pathogens had a significant death rate. [8] CRKP (44%) and CREC (26%) were the most prevalent carbapenem-resistant Gram-negative isolates in our investigation, with pneumonia or CLABSI accounting for more than half of all cases, similar to two prior Indian studies given as abstracts at scientific meetings. [9,10] Our patients had a high APACHE II score (19.64 3.8 SD) and spent an average of 11.76 days in the ICU, with a mean time to bacteremia onset of 6.4 days after admission. These findings are consistent with earlier research that has linked these microbes to healthcare-associated illnesses. [9]

Patients in intensive care units (ICUs) for extended periods of time frequently require central lines, dialysis catheters, broad-spectrum antibiotics, and mechanical ventilation, making them vulnerable to resistant hospital-acquired infections. Only 40% of our patients had received carbapenems, but nearly all had been exposed to antibiotics, implying that healthcare exposure and overall past antibiotic exposure may be more important risk factors for developing carbapenem resistant illnesses than carbapenem use. Colistin has become the cornerstone of therapy for carbapenem-resistant GNB, however the optimal dose and frequency of administration are still being researched.

Even with a mean eGFR of 52.48 ml/min at colistin beginning, the mean loading dose was only 5.14 million units, followed by a mean total daily dose of 5.18 million units intravenously. Low colistin doses may be used due to a fear of nephrotoxicity; our study period also preceded the development of new colistin dosing recommendations. Six patients (12%) required fresh onset RRT following colistin beginning due to worsening renal functions, however this was totally

reversible with dosage modifications, which was comforting and consistent with prior trials.

Our cohort's overall 30-day survival rate was only 40%, and it was difficult to determine whether this was related to sepsis or underlying severe disease and various co-morbidities. When CLABSI or VAP was the source of bacteremia, and CRAB and CRKP were the causal pathogens, our patients died the most. Although the west has reported higher survival rates, comparable results to ours have been seen in two earlier Indian abstract presentations. Higher colistin dosages were linked to better microbiologic clearance and lower mortality at 7 days, while death at 28 days did not vary. It's also plausible that the modest doses given to our patients led to their deaths.

We also saw that patients who received two treatment combinations had a greater survival rate than those who received colistin monotherapy, which has been found in other research. The lack of a statistically significant difference may be due to the small trial numbers in the two groups and the fact that more severely ill patients may undergo combination treatment.Our study has some limitations, including its retrospective character, limited sample size, and lack of a control group for comparison.

Conclusion

Carbapenem-resistant Gram-negative bacteremia is a significant healthcare-associated illness in critically ill patients with co-morbidities and past drug exposure in Indian ICUs; K. pneumoniae is the most prevalent pathogen at our facility. The 30-day survival rate is just 40% for CLABSI or VAP, and significantly worse when caused by A. baumanii or K. pneumoniae. Colistin is the cornerstone of therapy and may need to be examined at larger dosages to maximise the outcome; nephrotoxicity requiring RRT was only reported in 12% of patients and was completely reversible in all of them. Other antibiotics combined with colistin may result in reduced mortality than monotherapy, but this needs to be investigated further in a randomised controlled trial.

References

1. *Untreatable: Report by CDC details today's drug-resistant health threats.*
2. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:1–12.
3. Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hedge A, Soman R. New Delhi Metallo-beta lactamase (NDM-1) in *Enterobacteriaceae*: Treatment options with carbapenems compromised. *J Assoc Physicians India.* 2010;58:147–9.
4. Nair PK, Vaz MS. Prevalence of carbapenem resistant *Enterobacteriaceae* from a tertiary care hospital in Mumbai, India. *J Microbiol Infect Dis.* 2013;3:207–10.
5. Gupta E, Mohanty S, Sood S, Dhawan B, Das BK, Kapil A. Emerging resistance to carbapenems in a tertiary care hospital in North India. *Indian J Med Res.* 2006;124:95–8.

6. *Performance standards for antimicrobial susceptibility testing; Twenty-first informational supplement; M100-S21.* Wayne, PA: Clinical and Laboratory Standards Institute; 2011. Clinical and Laboratory Standards Institute.
7. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control.* 1988;16:128–40.
8. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med.* 2009;37:1463–9.
9. Parthasarathy P. Risk factors and mortality in carbapenem resistant gram negative bacteremias: A retrospective analysis from a tertiary health care setting in India. *Poster Abstract 1608, ID Week.* 2013
10. Ghafur A, Kannaian P, Tayade A. Clinical study of carbapenum-sensitive and carbapenem-resistant bacteraemia in neutropenic and non-neutropenic patients: The first series from India. *Abstract P 1368, 23rd ECCMID.* 2013