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Risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in a tertiary-care hospital in India

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To the Editor—*Klebsiella pneumoniae* is the second most frequently isolated organism from blood cultures after *Escherichia coli* in India, with 50% of all *K. pneumoniae* isolates being resistant to meropenem in 2019.¹ Infections due to carbapenem-resistant *K. pneumoniae* (CRKP) are difficult to treat and have serious implications for patient health and medical costs.² Two recent meta-analyses^{3,4} reported the risk factors of CRKP infections; however, none of the studies included in the meta-analyses were from India or South Asia, where CRKP infections are highly prevalent.⁵ The high burden of CRKP in Indian healthcare settings necessitates investigation into the risk factors for CRKP infections to identify potential interventions. Here, we examined the risk factors associated with CRKP bloodstream infections (BSIs) compared to carbapenem-sensitive *K. pneumoniae* (CSKP) BSIs in the Indian context.

A retrospective study was conducted at Medanta–The Medicity, a tertiary-care hospital with 1,500 beds in North India between August 2014 and July 2015. Patients with BSI caused by *K. pneumoniae* were included in the study. Only the first BSI with *K. pneumoniae* from a patient was included. Data were collected by reviewing medical records. The variables included demographics, admission diagnosis, ICU admission, comorbidities, exposure to invasive devices, immune status, prior exposure to antibiotics,

length of hospital stay and outcome. The blood-culture specimens were processed using BacT/Alert 3D (bioMérieux, Marcy l'Etoile, France) blood-culture system. Identification and antibiotic susceptibility testing was performed using a Vitek 2 compact instrument (bioMérieux, Marcy l'Etoile, France). The Clinical and Laboratory Standards Institute (CLSI 2015) break points were utilized.⁶ Categorical variables were reported as frequencies and percentages, and continuous variables were reported as medians and inter-quartile ranges. For univariate analyses, results were reported as odds ratios with 95% confidence intervals and P values. Variables with P values <.10 in the univariate analyses were included in backward, stepwise, logistic regression to determine the final multivariate logistic regression model to evaluate risk factors for CRKP. Statistical analyses were performed using SPSS Statistics 26 software (IBM, Armonk, NY). The study protocol was reviewed and approved by the institutional review board of Medanta Hospital, and the requirement for obtaining informed consent was waived because of the study's retrospective design.

Overall, during the study period, 111 patients had *K. pneumoniae* BSI. Of 111, 85 patients (77%) had CRKP and 26 patients (23%) had CSKP BSI. In univariate analysis, the following variables were associated with CRKP BSI: prior use of carbapenems, prior ICU stay, presence of foley catheter, mechanical ventilation, admission to ICU, prior use of polymyxins, admission to gastroenterology service and admission to liver transplant service (Table 1). However, in multivariate analysis, prior carbapenem use (odds ratio [OR], 7.04; 95% confidence interval [CI], 1.86–26.68; *P* = .004), presence of Foley catheter (OR-6.21; 95% CI- 1.61-23.98; *P* = .008) and admission to gastroenterology service

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Table 1. Univariate and Multivariate Analysis of Risk Factors Associated With Carbapenem-Resistant *K. pneumoniae* Bloodstream Infection (CRKP BSI)

Variable	Univariate Analysis				Multivariate Analysis	
	CRKP (n = 85)	CSKP (n = 26)	OR (CI)	P Value	OR (CI)	P Value
Demographics						
Age, years, mean (\pm SD)	55 (42–65)	57 (37.25–64.50)	1.01 (0.99–1.00)	.427		
Gender, male, n, (%)	67 (78.8)	19 (73.1)	1.08 (0.83–1.39)	.539		
Comorbid condition						
CCI score (\pm SD)	5 (3–6.50)	4.50 (3–7.25)	1.08 (0.90–1.30)	.41		
Diabetes mellitus	45 (52.9)	15 (57.7)	0.92 (0.62–1.44)	.671		
Invasive procedures or devices						
Invasive procedure	44 (51.8)	9 (34.6)	1.50 (0.85–2.64)	.126		
Intravenous catheter	85 (100)	25 (96.2)	N/A	.069		
Foleys catheter	71 (83.5)	15(57.7)	1.45 (1.03–2.04)	.006	6.21 (1.61–23.98)	.008
Mechanical ventilation	46 (54.1)	9(2.23)	1.56 (0.89–2.75)	.082		
Total parenteral nutrition	12 (14.1)	2(7.7)	1.83 (0.44–7.68)	.388		
Dialysis	29 (34.1)	5(19.2)	1.77 (.76–4.11)	.15		
Previous surgery ^a	21 (36.5)	6(23.1)	1.58 (0.74–3.36)	.205		
Admission in ICU	55 (64.7)	12 (46.2)	1.43 (0.92–2.22)	.071		
Prior hospitalization ^b	44 (51.8)	9 (34.6)	1.50 (0.85–2.64)	.126		
Prior ICU stay ^c	70 (82.4)	16 (61.5)	1.34 (0.97–1.84)	.026		
Hospitalization days, n, mean (\pm SD)	14 (10–26.50)	18 (8–28.50)	1.00 (0.98–1.02)	.86		
Immunosuppression						
Oncology	16 (18.8)	6 (23.1)	0.82 (0.36–1.87)	.634		
Transplant	23 (27.1)	3 (11.5)	2.34 (0.76–7.19)	.102		
Immunosuppressant drugs	28 (32.9)	5 (19.2)	1.71 (0.74–3.98)	.181		
Steroids	49 (57.6)	11 (42.3)	1.36 (0.84–2.21)	.17		
Prior receipt of antibiotics^d						
Carbapenems	49 (57.6)	6 (23.1)	2.50 (1.21–5.16)	.002	7.04 (1.86–26.68)	.004
Cephalosporins	57	17 (65.4)	1.03 (0.75–1.41)	.874		
Fluroquinolones	19 (22.4)	4 (15.4)	1.45 (0.54–3.89)	.443		
Glycopeptides	3 (3.5)	0 (0)	N/A	.331		
Glycylcyclines	3 (3.5)	0 (0)	N/A	.331		
Oxazolidinones	0 (0)	1 (3.8)	N/A	.069		
Polymyxins	14 (16.5)	0 (0)	N/A	.027		
Specialty under which patient was admitted						
Cardiology	7 (8.2)	0 (0)	N/A	.131		
Critical care	5 (5.9)	1 (3.8)	1.53 (0.19–12.51)	.688		
Hepatology	14 (16.5)	7 (26.9)	0.61 (.28–1.35)	.234		
Gastroenterology	15 (17.6)	1 (3.8)	4.59 (0.64–33.01)	.08	9.85 (1.00–96.97)	.05
Liver transplant	11 (12.9)	0 (0)	N/A	.053		
Nephrology	9 (10.6)	4 (15.4)	0.69 (0.23–2.05)	.506		
Neurology	7 (8.2)	3 (11.5)	0.71 (0.20–2.56)	.607		
General surgery	6 (7.1)	3 (11.5)	0.61 (0.16–2.28)	.464		
Med-oncology	9 (10.6)	2 (7.7)	1.38 (0.32–5.97)	.665		
Internal medicine	1 (1.2)	2 (7.7)	0.15 (0.014–1.62)	.073		
Pulmonology	1 (1.2)	1 (3.8)	0.31 (0.02–4.72)	.37		

Note. CCI, Charlson comorbidity index; OR, odds ratio; CI, confidence interval; CSKP, carbapenem-susceptible KP; ICU, intensive care unit; KP, *Klebsiella pneumoniae*; SD, standard deviation.

^aSurgery within 30 days prior to collection of blood culture.

^bHospitalization within 3 months prior to collection of blood culture.

^cICU admission within 30 days prior to collection of blood culture.

^dThe exposure had occurred during the current hospitalization before the blood culture was obtained or previous hospitalization within 30 days and a systemic antibiotic was administered for at least 1 day.

(OR, 9.85; 95% CI, 1.00–96.97; $P = .05$) were associated with CRKP BSI (Table 1). The in-hospital mortality rates were 42.4% (36 of 85) and 23.1% (6 of 26) among CRKP and CSKP patients, respectively. In univariate analysis the in-hospital mortality was higher in CRKP patients (OR, 1.21; 95% CI, 0.99–1.47; $P = .07$); however, it was not statistically significant in multivariate analysis.

To our knowledge, this is the first study to report on the risk factors associated with CRKP infections in India. Our findings are consistent with the 2 recent meta-analyses that reported carbapenem exposure and the presence of Foley catheter as risk factors for CRKP infections. Two other factors, namely mechanical ventilation and admission to ICU, which were identified as risk factors in meta-analyses, were significant in univariate analyses but not in multivariate analysis. This could be due to our small sample size. A recent prospective study conducted in several low- and middle-income countries (LMICs) reported increased in-hospital mortality with carbapenem-resistant *Enterobacteriales* (CRE) BSIs.⁷ We observed higher mortality in univariate analysis but not in multivariate analysis, which could also be related to the small sample size of our study.

We observed that patients admitted to gastroenterology service had higher odds of CRKP BSI. The gastrointestinal tract is a site for *K. pneumoniae* colonization,⁸ and patients admitted to gastroenterology units are inflicted with erosive or inflammatory pathology; mucosal damage can predispose them to translocation of gut flora into the bloodstream. Contaminated endoscopes have been causally linked to multidrug-resistant organism outbreaks in the past⁹; however, we did not capture the number of endoscopic procedures among CRKP and CSKP patients. Moreover, the increased use of carbapenems in this patient subset can further contribute to the high rate of CRKP infections. However, the 95% confidence interval for the odds ratio is wide, reflecting that the need for a bigger sample size to confirm this association.

The high burden of CRKP BSI in Indian hospitals is of concern because there are no effective antibiotic treatment options. None of the recently approved antibiotics¹⁰ are active against the New-Delhi metallo- β -lactamase-producing strains of CRE, which are highly prevalent in India.¹ Our findings reinforce the need for appropriate use of carbapenems and infection control practices in Indian hospitals. There is an urgent need for effective interventions aimed at improving antimicrobial stewardship and infection

preventions programs in Indian healthcare settings to effectively manage CRKP BSIs.

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