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Original Research Article

CLINICAL EPIDEMIOLOGY AND RISK FACTORS OF CARBAPENEM-RESISTANT GRAM-NEGATIVE BLOODSTREAM INFECTIONS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Background: The objective is to determine the clinical epidemiology, microbiological profile, and risk factors associated with carbapenem-resistant Gram-negative bloodstream infections (CR-GNBSIs) among patients with hematological malignancies in tertiary care hospitals of Pakistan.

Materials and Methods: This multicenter analytical cross-sectional study was conducted in the Departments of Hematology and Microbiology of three tertiary care hospitals in Pakistan from January to December 2025. Adult patients with hematological malignancies and culture-confirmed Gram-negative bloodstream infections were enrolled through consecutive sampling. Blood cultures were processed using standard microbiological techniques, and antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method according to Clinical and Laboratory Standards Institute guidelines. Demographic, clinical, microbiological, and treatment-related variables were recorded. Risk factors associated with carbapenem resistance were identified using logistic regression analysis.

Results: A total of 220 patients with Gram-negative bloodstream infections were included. The mean age was 43.8±15.6 years, and 128 (58.2%) were male. Carbapenem-resistant isolates were identified in 76 (34.5%) cases. The most frequently isolated organisms were Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa. Prior exposure to broad-spectrum antibiotics (adjusted odds ratio [AOR]: 3.12, 95% CI: 1.65–5.89), prolonged neutropenia exceeding seven days (AOR: 2.84, 95% CI: 1.47–5.49), intensive care unit admission (AOR: 2.56, 95% CI: 1.23–5.31), and central venous catheter use (AOR: 2.21, 95% CI: 1.12–4.37) were independently associated with carbapenem resistance. Patients with CR-GNBSIs had significantly higher in-hospital mortality than those with carbapenem-susceptible infections (38.2% vs. 18.1%, $p<0.001$).

Conclusion: Carbapenem-resistant Gram-negative bloodstream infections are common among patients with hematological malignancies and are associated with substantial mortality. Previous antibiotic exposure, prolonged neutropenia, intensive care admission, and central venous catheterization were significant predictors of carbapenem resistance.

Keywords: Hematological malignancies, bloodstream infection, carbapenem resistance, Gram-negative bacteria, neutropenia, Pakistan.

INTRODUCTION

Bloodstream infections (BSIs) remain one of the most serious infectious complications among patients with hematological malignancies and are a major cause of morbidity, prolonged hospitalization, interruption of chemotherapy, and mortality.[1] The profound immunosuppression associated with hematological cancers, together with disease-related immune dysfunction, intensive chemotherapy, prolonged neutropenia, mucosal barrier injury, and the frequent use of invasive medical devices, substantially increases susceptibility to severe bacterial infections.[2] Although advances in supportive care have improved overall survival, infectious complications continue to represent a major obstacle to successful treatment, particularly in low- and middle-income countries (LMICs), where limited diagnostic facilities and restricted access to newer antimicrobial agents further complicate patient management.[1,2]

During the past two decades, the epidemiology of bloodstream infections in patients with hematological malignancies has shifted toward a predominance of Gram-negative organisms. Members of the Enterobacterales family, particularly Klebsiella pneumoniae and Escherichia coli, together with non-fermenting bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii, have emerged as the leading pathogens causing severe sepsis in neutropenic patients.[3] These infections are often characterized by rapid clinical deterioration, septic shock, and high mortality, emphasizing the importance of prompt microbiological diagnosis and timely administration of appropriate empirical antimicrobial therapy.[4]

The emergence and rapid dissemination of carbapenem-resistant Gram-negative bacteria have become one of the most pressing challenges in contemporary hematology practice.[5] Carbapenems have traditionally served as the cornerstone of empirical treatment for severe infections caused by multidrug-resistant Gram-negative organisms. However, increasing resistance to these agents has significantly compromised therapeutic options and has been associated with delayed initiation of effective antimicrobial therapy, prolonged hospital stay, greater healthcare costs, and increased mortality.[6] Patients with hematological malignancies are particularly vulnerable because repeated hospitalizations and frequent exposure to broad-spectrum antibiotics create substantial selective pressure favoring the emergence of resistant pathogens.[5]

Several factors increase the risk of carbapenem-resistant bloodstream infections in patients with hematological malignancies, including prior broad-spectrum antibiotic exposure, prolonged neutropenia, chemotherapy, prolonged hospitalization, ICU admission, and central venous catheterization.[7] Early identification of these risk factors is essential for optimizing empirical antibiotic therapy, enhancing infection prevention, and strengthening antimicrobial stewardship, particularly in resource-limited settings.[8]

The burden of antimicrobial resistance is particularly high in low- and middle-income countries such as Pakistan, where inappropriate antibiotic use, inadequate infection control, and limited antimicrobial stewardship accelerate the spread of resistant pathogens.[9] Although carbapenem-resistant Gram-negative bloodstream infections are increasingly reported in South Asia, data on their risk factors among Pakistani patients with hematological malignancies remain limited.[10] Understanding the local epidemiology of carbapenem-resistant Gram-negative bloodstream infections is essential because bacterial species distribution and antimicrobial resistance patterns vary considerably across geographic regions and healthcare institutions. Local epidemiological data facilitate the development of evidence-based empirical antibiotic policies, guide antimicrobial stewardship initiatives, and support infection control interventions aimed at reducing the spread of resistant organisms.[11] Furthermore, identification of modifiable clinical risk factors may enable clinicians to recognize high-risk patients early, optimize antimicrobial therapy, and improve clinical outcomes while minimizing unnecessary exposure to broad-spectrum antibiotics.[11,12]

The present study was therefore undertaken to determine the clinical epidemiology of carbapenem-resistant Gram-negative bloodstream infections among adults with hematological malignancies treated at tertiary care hospitals in Pakistan. In addition, the study aimed to identify clinical and treatment-related factors independently associated with carbapenem resistance and to evaluate the microbiological spectrum and clinical outcomes of these infections. The findings are expected to provide locally relevant evidence to support empirical antibiotic selection, antimicrobial stewardship, and infection prevention strategies in hematology units operating in resource-limited settings.

MATERIALS AND METHODS

This study was conducted as a narrative review to explore and analyze the evolving implications of the Consumer Protection Act (CPA) on medical practice in India. The literature search was performed using multiple academic and legal databases, including PubMed, Google Scholar, JSTOR, Indian Kanoon, and the official portals of the National Consumer Disputes Redressal Commission (NCDRC) and Supreme Court of India. The search strategy focused on retrieving relevant scholarly articles, case laws, review papers, and legal analyses published between 2010 and 2024.

Table 1: Operational definitions of study variables:

Variable	Operational definition
Bloodstream infection	Isolation of a clinically significant Gram-negative organism from at least one blood culture in a patient with compatible clinical features of infection
Carbapenem resistance	Resistance to imipenem and/or meropenem according to CLSI 2025 criteria
Neutropenia	Absolute neutrophil count <500 cells/mm³ or expected decline below 500 cells/mm³ within 48 hours
Prolonged neutropenia	Duration of neutropenia >7 consecutive days
Febrile neutropenia	Single oral temperature ≥38.3°C or ≥38.0°C sustained for one hour with neutropenia
Previous broad-spectrum antibiotic exposure	Administration of carbapenems, fourth-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations, or fluoroquinolones for ≥48 hours within the preceding 90 days
Previous hospitalization	Hospital admission for ≥48 hours within the previous 90 days
Clinical outcome	Survival or in-hospital mortality at the end of hospitalization

RESULTS

A total of 232 adult patients with hematological malignancies and culture-confirmed Gram-negative bloodstream infections were included. Carbapenem-resistant Gram-negative bloodstream infections (CR-GNBSIs) accounted for approximately one-third of all cases. Acute myeloid leukemia was the most frequent underlying hematological malignancy. Most patients had recently received chemotherapy, and febrile neutropenia was common. Baseline demographic and clinical characteristics are summarized in [Table 2].

Table 2. Baseline demographic and clinical characteristics of study participants (n=232)

Variable	n (%)
Age (years), mean ± SD	44.1 ± 15.8
Male	136 (58.6)
Female	96 (41.4)
Underlying malignancy	
Acute myeloid leukemia	94 (40.5)
Acute lymphoblastic leukemia	48 (20.7)
Chronic myeloid leukemia	21 (9.1)
Chronic lymphocytic leukemia	12 (5.2)
Non-Hodgkin lymphoma	31 (13.4)
Hodgkin lymphoma	8 (3.4)
Multiple myeloma	12 (5.2)
Myelodysplastic syndrome/others	6 (2.6)
Chemotherapy within previous 30 days	171 (73.7)
Febrile neutropenia	162 (69.8)
Prolonged neutropenia (>7 days)	108 (46.6)
Central venous catheter	104 (44.8)
ICU admission	52 (22.4)
Previous broad-spectrum antibiotic exposure	124 (53.4)
Previous hospitalization	97 (41.8)
Carbapenem-resistant infection	80 (34.5)

Klebsiella pneumoniae was the predominant bloodstream isolate, followed by Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii. The distribution of isolates and their carbapenem-resistance patterns are presented in [Table 3].

Table 3: Distribution of Gram-negative bacterial isolates

Organism	Total isolates n (%)	Carbapenem-resistant n (%)
Klebsiella pneumoniae	82 (35.3)	32 (39.0)
Escherichia coli	61 (26.3)	12 (19.7)
Pseudomonas aeruginosa	43 (18.5)	14 (32.6)
Acinetobacter baumannii	28 (12.1)	17 (60.7)
Enterobacter cloacae	12 (5.2)	4 (33.3)
Citrobacter freundii	6 (2.6)	1 (16.7)
Total	232 (100)	80 (34.5)

Carbapenem-resistant isolates demonstrated limited susceptibility to several routinely used antimicrobial agents. The antimicrobial susceptibility profile is shown in [Table 4].

Table 4: Antimicrobial susceptibility pattern among carbapenem-resistant isolates (n=80)

Antibiotic	Sensitive n (%)
Amikacin	38 (47.5)
Gentamicin	25 (31.3)
Ciprofloxacin	14 (17.5)
Piperacillin–tazobactam	18 (22.5)
Cefepime	11 (13.8)
Ceftazidime	9 (11.3)

Cefoperazone–sulbactam	28 (35.0)
Trimethoprim–sulfamethoxazole	20 (25.0)
Colistin	77 (96.3)

Several clinical and healthcare-related factors showed significant associations with carbapenem resistance on univariate analysis. These comparisons are presented in [Table 5].

Table 5: Univariate analysis of factors associated with carbapenem-resistant bloodstream infections

Variable	CR-GNBSI (n=80)	CS-GNBSI (n=152)	p-value
Male gender	49 (61.3%)	87 (57.2%)	0.551
Age >60 years	21 (26.3%)	31 (20.4%)	0.305
Chemotherapy within previous 30 days	67 (83.8%)	104 (68.4%)	0.014
Previous broad-spectrum antibiotics	61 (76.3%)	63 (41.4%)	<0.001
Prolonged neutropenia	52 (65.0%)	56 (36.8%)	<0.001
Central venous catheter	49 (61.3%)	55 (36.2%)	<0.001
ICU admission	31 (38.8%)	21 (13.8%)	<0.001
Previous hospitalization	45 (56.3%)	52 (34.2%)	0.001

Multivariable logistic regression identified previous broad-spectrum antibiotic exposure, prolonged neutropenia, ICU admission, and central venous catheterization as independent predictors of CR-GNBSI. The adjusted estimates are presented in [Table 6].

Table 6: Multivariable logistic regression analysis of independent risk factors for CR-GNBSI

Variable	Adjusted odds ratio (AOR)	95% CI	p-value
Previous broad-spectrum antibiotic exposure	3.18	1.69–5.97	<0.001
Prolonged neutropenia (>7 days)	2.76	1.48–5.17	0.001
ICU admission	2.43	1.16–5.10	0.018
Central venous catheter	2.15	1.13–4.08	0.021
Chemotherapy within previous 30 days	1.62	0.81–3.23	0.173
Previous hospitalization	1.48	0.79–2.78	0.218

Patients with CR-GNBSI had a longer median hospital stay than those with carbapenem-susceptible infections (21 [IQR 16–29] versus 15 [IQR 11–21] days; p<0.001). In-hospital mortality was also higher in the CR-GNBSI group (38.8% versus 18.4%; p=0.001).

DISCUSSION

The present multicenter study evaluated the clinical epidemiology and risk factors of carbapenem-resistant Gram-negative bloodstream infections (CR-GNBSIs) among patients with hematological malignancies in Pakistan. Approximately one-third (34.5%) of bloodstream infections were caused by carbapenem-resistant organisms, highlighting the growing burden of antimicrobial resistance in this vulnerable population. Patients with hematological malignancies are particularly susceptible to severe bacterial infections because of prolonged neutropenia, repeated chemotherapy, disruption of mucosal barriers, and frequent healthcare exposure.[13] Our findings indicate that carbapenem resistance has become a significant therapeutic challenge in hematology units, particularly in resource-limited settings where access to newer antimicrobial agents remains restricted.[13,14]

Klebsiella pneumoniae was the predominant pathogen isolated, followed by Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii [Table 3]. This distribution is consistent with recent studies from Asia and other low- and middle-income countries, where Enterobacterales have emerged as the leading cause of bloodstream infections among immunocompromised patients.[15] The high proportion of carbapenem resistance observed among Acinetobacter baumannii and Klebsiella pneumoniae is particularly concerning because these pathogens are associated with limited therapeutic options and poor clinical outcomes.[16]

The antimicrobial susceptibility profile demonstrated extensive resistance to cephalosporins, fluoroquinolones, and β-lactam/β-lactamase inhibitor combinations among carbapenem-resistant isolates (Table IV). Colistin retained excellent in vitro activity, while amikacin showed moderate susceptibility. Similar resistance patterns have been reported in South Asian surveillance studies and reflect the widespread use of broad-spectrum antibiotics in tertiary care hospitals.[17] These findings underscore the importance of continuous antimicrobial resistance surveillance and the development of institution-specific antibiograms to guide empirical antibiotic therapy in hematology patients.[18]

The present study identified several independent predictors of carbapenem-resistant bloodstream infections. Previous exposure to broad-spectrum antibiotics was the strongest independent risk factor [Table 6], emphasizing the role of antimicrobial selection pressure in the emergence of resistant pathogens. Prolonged neutropenia, central venous catheterization, and ICU admission were also independently associated with carbapenem resistance. These observations are in agreement with previous studies, which have consistently demonstrated that prolonged hospitalization, invasive procedures, and repeated exposure to

broad-spectrum antimicrobials facilitate colonization and subsequent infection with resistant Gram-negative bacteria.[19,20]

Patients with carbapenem-resistant infections experienced significantly longer hospital stays and higher in-hospital mortality compared with those infected by carbapenem-susceptible organisms. Delayed administration of effective antimicrobial therapy, severe underlying immunosuppression, and limited availability of active treatment options may explain these poorer outcomes. Early recognition of high-risk patients, prompt microbiological diagnosis, implementation of antimicrobial stewardship programs, and strict infection prevention measures are essential to reduce the burden of carbapenem-resistant infections in hematology units.[21]

This study's strengths include its multicenter design and the use of standardized microbiological methods. This study provides valuable local evidence regarding the epidemiology and determinants of carbapenem-resistant Gram-negative bloodstream infections in Pakistan and support the implementation of antimicrobial stewardship, strict infection prevention practices, and evidence-based empirical antibiotic policies to curb the spread of multidrug-resistant Gram-negative pathogens in hematology units.

CONCLUSION

Carbapenem--resistant Gram-negative bloodstream infections were common among patients with hematological malignancies and were associated with increased mortality and prolonged hospitalization. Previous broad-spectrum antibiotic exposure, prolonged neutropenia, ICU admission, and central venous catheterization were significant independent risk factors. Strengthening antimicrobial stewardship, infection prevention practices, and early identification of high-risk patients may help reduce the burden and improve clinical outcomes of these infections in resource-limited settings.

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