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IDENTIFYING THE RISK FACTORS FOR INFECTION WITH MULTIDRUG-RESISTANT GRAM-NEGATIVE PATHOGENS: A CASE CONTROL STUDY FROM AYUB TEACHING HOSPITAL & MUSHARRAF MEDICAL COMPLEX, PAK.

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Abstract

Background: The rising prevalence of multidrug-resistant (MDR) Gram-negative bacteria (GNB) in healthcare settings poses a significant challenge to infection control and patient safety. This study aims to identify key risk factors associated with MDR infections caused by pathogens such as *Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Escherichia coli*. Understanding these risk factors is crucial for developing effective containment strategies and guiding healthcare professionals in implementing targeted infection control measures. Additionally, recognizing patterns of resistance can aid in optimizing antimicrobial stewardship programs and improving patient outcomes.

Methods: A case-control study was conducted at Ayub Teaching Hospital and Musharraf Medical Complex, Abbottabad, to evaluate the risk factors associated with multidrug-resistant (MDR) Gram-negative bacterial infections in hospitalized patients. The study included two groups: 200 patients with healthcare-associated infections (HAIs) due to MDR Gram-negative bacteria and 200 patients with HAIs caused by non-MDR Gram-negative bacteria (organisms not meeting MDR criteria). HAIs were defined as infections developing 48 hours or more after hospital admission. MDR bacteria were categorized as those resistant to at least one antibiotic in three or more antimicrobial classes. Data were analyzed using descriptive statistics to determine the frequency and percentage distribution of categorical variables. Multivariate regression analysis was applied to identify independent risk factors for MDR infections, with statistical significance set at a p-value of <0.05.

Results: Over a four-month period (March–June 2024), a total of 529 bacterial isolates were recovered from 452 hospitalized patients at Ayub Teaching Hospital and Musharraf Medical Complex, Abbottabad. Among these patients, 77(17%) had polymicrobial infections caused by more than one pathogen.Among the multidrug-resistant (MDR) isolates, *Acinetobacter baumannii* was the most prevalent (38%), followed by *Klebsiella pneumoniae* (31%,), *Pseudomonas aeruginosa* (20%), and *Escherichia coli* (11%). Conversely, among the non-MDR isolates, *Pseudomonas aeruginosa* was the most frequently identified (47%), followed by *Escherichia coli* (32%), *Klebsiella pneumoniae* (18%,), and *Acinetobacter baumannii* (3%).A comparative analysis between MDR-infected patients and those infected with non-MDR organisms revealed that prior antibiotic use ($p = 0.001$), intensive care unit (ICU) admission ($p = 0.001$), and the presence of indwelling medical devices ($p = 0.005$) were significant predictors of MDR infections. These findings highlight the critical role of antimicrobial stewardship and infection control measures in limiting the emergence and spread of MDR pathogens in hospitalized patients.

Conclusion: The findings underscore the growing threat of MDR infections in Pakistani hospitals, where excessive antibiotic use, prolonged hospitalization, and inadequate infection control practices contribute to the problem. By minimizing unnecessary antibiotic use, improving hospital hygiene, and ensuring strict adherence to infection prevention protocols—especially in high-risk areas like intensive care units—healthcare facilities in Pakistan can reduce the burden of MDR infections. Strengthening surveillance systems and promoting awareness among medical staff can further aid in controlling the emergence and transmission of these resistant pathogens, ultimately improving patient safety and treatment outcomes.

Keywords: Hospital-acquired infections, colonization, infection risk factors, antimicrobial resistance, multidrug-resistant (MDR) bacteria, Gram-negative pathogens,

Introduction

Multidrug resistance (MDR) remains one of the leading challenges in the health care system worldwide. Studies have shown that approximately 4.71 million deaths worldwide were attributable to bacterial Multidrug resistance in 2021 alone. This figure is expected to rise to 8.22 million by year 2050[1]. In developing countries, problems related to MDR Gram negative bacterial (GNB) infections have yet to be addressed effectively. In Pakistan, a recent study reported a 36% increase in MDR in 2024[2]. This might be the result of extensive misuse of antibiotics, which is exacerbated by inadequate drug regulation.World Health Organisation (WHO) has released its updated Priority Bacterial Pathogens List (2024) featuring 15 families of MDR bacteria, which are grouped into critical, high and medium priority categories. The critical priority includes *Acinetobacter baumannii*, carbapenem-resistant, Enterobacterales, third-generation cephalosporin-resistant and Enterobacterales, carbapenem-resistant. The high priority includes *Salmonella Typhi*, fluoroquinolone-resistant, *Shigella* spp., fluoroquinolone-resistant, *Enterococcus faecium*, vancomycin-resistant,*Pseudomonas aeruginosa*, carbapenem-resistant and the medium category consists of *Haemophilus influenzae*, ampicillin-resistant [3]. Studies have reported resistance rates of up to 30% to carbapenems, 30-50% to third-generation cephalosporins, fluoroquinolones and more than 50% to aminoglycosides in gram negative organisms[4].This resistance can be developed through a multitude of well known mechanisms.GNB, in particular, can develop antibiotic resistance through following mode: drug inactivation, limiting drug intake. altering drug target and high level of drug efflux.Within these modes there is a wide array of mechanisms including antibiotics inactivation/modulation, limiting influx of antibiotics, modification of antibiotic target, 16s ribosomal RNA methylation, among others.[5]Despite the critical severity of this problem, there is still a major lack of research in MDR to GNB infections in the country. The unavailability of localized data poses a significant challenge to health care workers in combating MDR-GNB infections. Key risk factors contributing to MDR-GNB infections include prolonged hospital stays, indirect person-to-person contact, treatment with glycopeptides or broad spectrum antibiotics, urinary catheterization, excessive use of antibiotics, and contamination of humidifiers and nebulisers. [6] Identifying the risk factors and formulating evidence-based guidelines is expected to reduce the mortality associated with MDR-GNB. This will shorten the stay of patients in hospitals. The overall healthcare cost can be decreased in a country with a predominantly low socioeconomic class. The availability of relevant data will help clinicians in effective treatments. Such strategy is aimed to reduce the overall burden of MDR-GNB infections and improving patient outcomes.

Study Design and Setting

This study was conducted over a four-month period (March to June 2024) at Ayub Teaching tertiary care Hospital, and Musharraf Medical Complex, Abbottabad. Bacterial isolates were prospectively collected from routine clinical samples of patients diagnosed with bloodstream infections, respiratory tract infections, skin and soft tissue infections, and urinary tract infections. The study focused on four key Gram-negative pathogens: Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli. Only isolates from healthcare-associated infections (HAIs), defined as infections occurring 48 hours or more after hospital admission, were included in the study. To maintain accuracy, each organism was recorded only once at the time of the first positive culture.Both multidrug-resistant (MDR) and non-MDR Gram-negative bacteria (GNB) were studied, with non-MDR organisms classified as those not meeting the MDR criteria. The definition of MDR was based on international guidelines from the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), where MDR organisms were identified as those resistant to at least one antibiotic in three or more antimicrobial classes. Bacterial isolates were tested for antibiotic susceptibility using the automated Vitek® 2 System (bioMérieux, USA), with results interpreted following Clinical and Laboratory Standards Institute (CLSI) guidelines. A case-control study design was employed to analyze significant risk factors associated with MDR infections. The study population consisted of 400 hospitalized patients, divided into two equal groups:

- Cases (100 patients): Patients infected with MDR GNB.
- Control group (100 patients): Patients with infections caused by non-MDR GNB.

Patients were selected based on admission date, microbiological culture results, and clinical assessment. For each patient, detailed clinical data were systematically recorded, including:

- Primary diagnosis at admission.
- Hospital ward (medical, surgical, or ICU).
- Antimicrobial use within the past 90 days.
- History of hospitalization within the past 90 days.
- Prolonged hospital stay (≥ 5 days).
- ICU admission.
- Immunosuppressive conditions, including active malignancy, chemotherapy, post-organ transplant on immunosuppressive therapy (including steroids), and HIV-positive status with CD4 < 200.
- Presence of indwelling medical devices (e.g., central lines, urinary catheters, ventilators).
- Recent surgery or trauma within the past 90 days.
- Age ≥ 60 years.
- Gender and emergency admission status.

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as means ± standard deviations (SD) or medians with interquartile ranges (IQRs), depending on data distribution (assessed using the Shapiro-Wilk test). Categorical variables were presented as frequencies and percentages, and comparisons between groups were conducted using the chi-square test or Fisher's exact test, as appropriate. For continuous variables, the independent t-test or Mann-Whitney U test was used.

Matching and Confounder Adjustment

To minimize selection bias, cases (patients with HAIs due to MDR Gram-negative bacteria) and controls (patients with HAIs due to non-MDR Gram-negative bacteria) were matched based on hospital ward, admission period, age (±5 years), sex, and presence of major comorbidities (diabetes, chronic kidney disease, malignancy, and immunosuppression status). This ensured a more balanced comparison between groups**.** Matching adjustments were verified using standardized mean differences (SMDs), with values <0.1 considered acceptable.

Power Analysis

A power calculation was performed to determine the adequacy of the sample size. Based on prior literature, an expected OR of 3.0 for significant risk factors (e.g., prior antibiotic use) was assumed, with a control group prevalence of exposure of ~30%. To achieve 80% power with a two-sided alpha of 0.05**,** at least 170 patients per group were required. Our study, **with** 200 cases and 200 controls, met this requirement.

Multivariable Logistic Regression & Multicollinearity Check

Multivariable logistic regression was performed to identify independent risk factors for MDR infections. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated. Multicollinearity was assessed using Variance Inflation Factors (VIFs), with a threshold of VIF >5 indicating collinearity. No significant multicollinearity was found among predictor variables, ensuring the reliability of the regression model.The variables included in the regression model were: Prior antimicrobial use within the past 90 days, Previous hospitalization within the last 90 days, Prolonged hospital stay (≥5 days),ICU admission, Immunosuppressed status, Presence of indwelling medical devices, History of recent surgery or trauma within the past 90 days, Gender and emergency admission status. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the strength of association between these risk factors and MDR infections. A p-value of <0.05 was considered statistically significant.

Results

Between March and June 2024, a total of 529 Gram-negative bacterial (GNB) isolates were obtained from routine clinical specimens of 452 hospitalized patients at Ayub Teaching Hospital and Musharraf Medical Complex. Among these, 77 patients (17%) harbored more than one organism. As per the study criteria, only bacteria associated with healthcare-acquired infections (HAIs) were included.The predominant pathogens were Acinetobacter baumannii (201 isolates, 38%), Klebsiella pneumoniae (140 isolates, 31%), Pseudomonas aeruginosa (106 isolates, 20%), and Escherichia coli (58 isolates, 11%). These isolates were evenly divided between multidrug-resistant (MDR) GNB (264 isolates) and non-MDR GNB (265 isolates).Among the MDR organisms, the most frequently isolated pathogen was A. baumannii (100 isolates, 38%), followed by K. pneumoniae (82 isolates, 31%), P. aeruginosa (53 isolates, 20%), and E. coli (29 isolates, 11%). In contrast, among the non-MDR bacterial isolates, P. aeruginosa (125 isolates, 47%) was the most common, followed by E. coli (85 isolates, 32%), K. pneumoniae (48 isolates, 18%), and A. baumannii (8 isolates, 3%).Among the 200 patients infected with MDR bacteria, 102 (51%) were male and 98 (49%) were female; 142 (71%) were emergency admissions, while 58 (29%) were elective hospitalizations. Similarly, among the 200 patients infected with non-MDR organisms, 116 (58%) were male and 84 (42%) were female, with 120 (60%) admitted through emergency and 80 (40%) through elective hospitalization.In the overall case-control study involving 400 patients, 192 (48%) were male and 208 (52%) were female, while 196 (49%) were aged 60 years or older. A significant proportion, 316 patients (79%), were admitted through the emergency department, while 84 patients (21%) underwent elective admissions.Several risk factors were observed across the study groups:

- 248 patients (62%) had received antimicrobial therapy in the previous 90 days.
- 148 patients (37%) had been hospitalized within the last three months.

- 268 patients (67%) experienced prolonged hospital stays (≥5 days).
- 92 patients (23%) had ICU admissions.
- 96 patients (24%) were receiving immunosuppressive therapy (chemotherapy, post-organ transplant medications, or HIV with CD4 < 200).
- 220 patients (55%) had indwelling medical devices (such as catheters, central lines, or mechanical ventilation).
- 140 patients (35%) had a history of recent surgery or trauma in the previous 90 days.

A statistical analysis comparing MDR-infected patients with non-MDR-infected patients revealed three major risk factors:

- Prior antibiotic use significantly increased the risk of MDR infections (Odds Ratio [OR]: 5.50, 95% CI: 2.19–13.84, p-value: 0.001).
- ICU admission was strongly associated with MDR infections (OR: 11.11, 95% CI: 4.58–26.93, p-value: 0.001).
- Presence of indwelling medical devices posed a notable risk (OR: 3.02, 95% CI: 1.45–6.33, p-value: 0.005).

Table 1: Gender and Admission Type Distribution among Study Groups

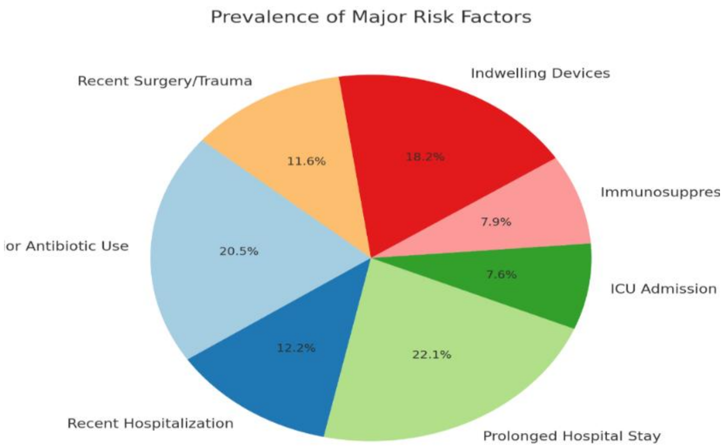
Study Group	Total Patients	Males (%)	Females (%)	Emergency Admissions (%)	Elective Admissions (%)
MDR-Infected	200	102 (51%)	98 (49%)	142 (71%)	58 (29%)
Non-MDR Infected	200	116 (58%)	84 (42%)	120 (60%)	80 (40%)
Total (All Groups)	400	218 (54.5%)	182 (45.5%)	262 (65.5%)	138 (34.5%)

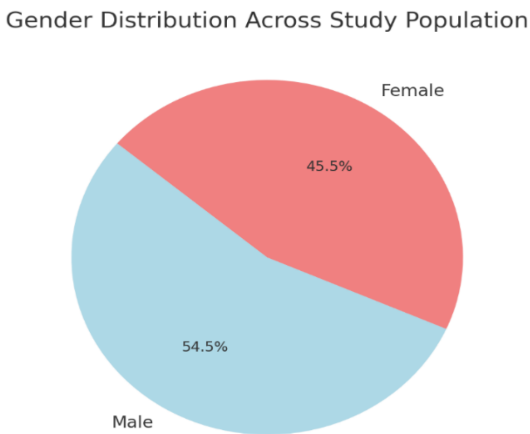
Table 2: Prevalence of Risk Factors across the Study Population

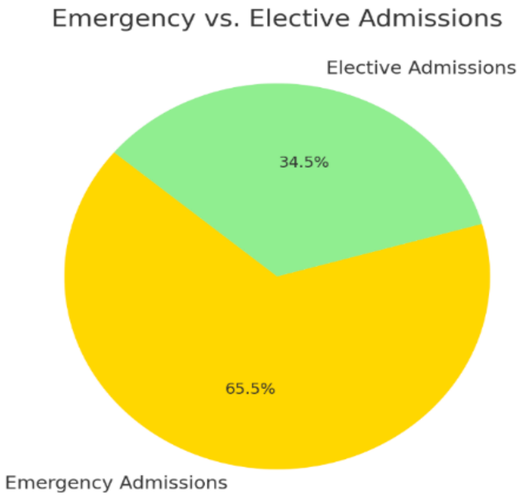
Risk Factor	Total Patients Affected	Percentage (%)
Prior antibiotic use	248	62%
Recent hospitalization (<3 months)	148	37%
Prolonged hospital stay (≥5 days)	268	67%
ICU admission	92	23%
Immunosuppressive therapy	96	24%
Indwelling medical devices	220	55%
Recent surgery/trauma (<90 days)	140	35%

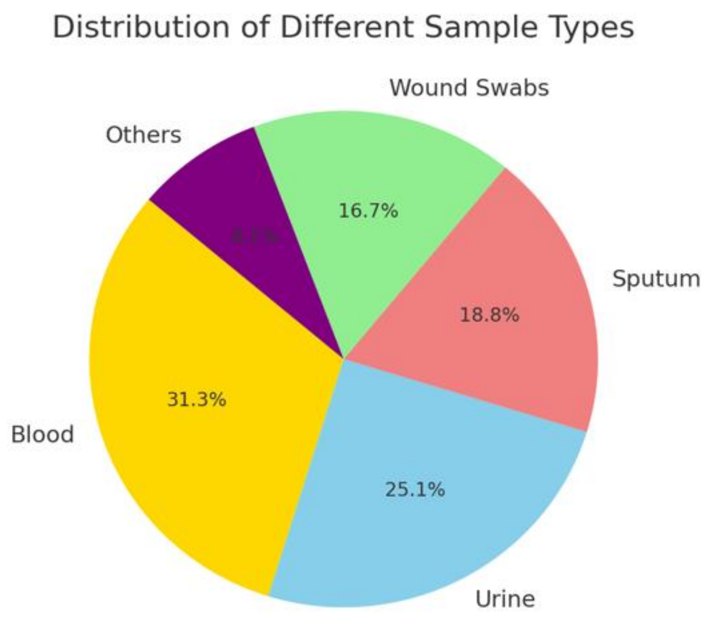
Table 3: Comparison of Significant Risk Factors between MDR and Non-MDR Infections

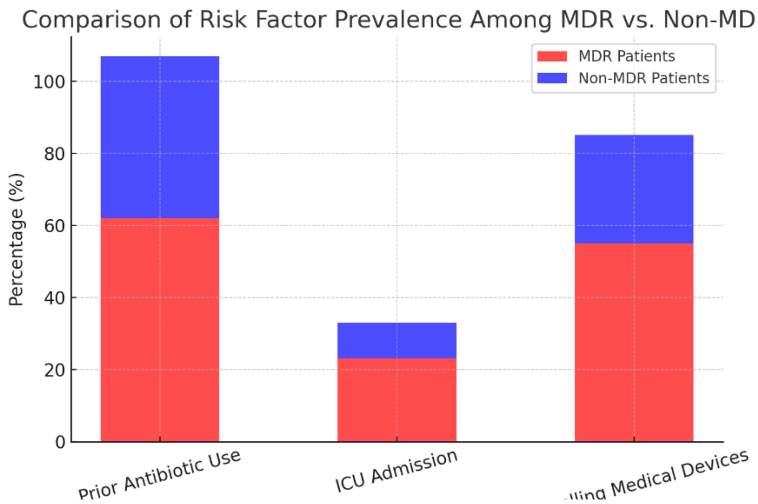
Risk Factor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Prior antibiotic use	5.50	2.19–13.84	0.001**
ICU admission	11.11	4.58–26.93	0.001**
Indwelling medical devices	3.02	1.45–6.33	0.005**

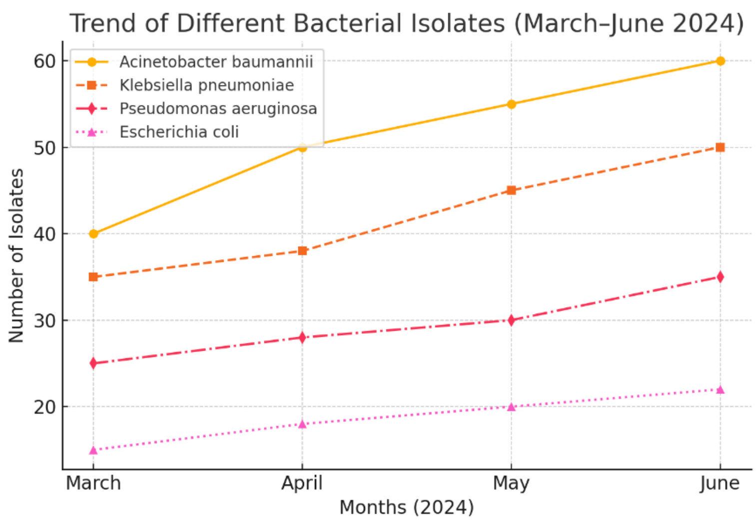

Prevalence of Major Risk Factors
Recent Surgery/Trauma
Indwelling Devices
Immunosuppres
or Antibiotic Use
ICU Admission
Recent Hospitalization
Prolonged Hospital Stay
11.6%
18.2%
7.9%
20.5%
7.6%
12.2%
22.1%


Gender Distribution Across Study Population
Female
45.5%
54.5%
Male


Emergency vs. Elective Admissions
Elective Admissions
34.5%
65.5%
Emergency Admissions


Distribution of Different Sample Types
Wound Swabs
Others
16.7%
Sputum
18.8%
31.3%
Blood
25.1%
Urine


Comparison of Risk Factor Prevalence Among MDR vs. Non-MDR
MDR Patients
Non-MDR Patients
Percentage (%)
0
20
40
60
80
100
Prior Antibiotic Use
ICU Admission
Medical Devices


Trend of Different Bacterial Isolates (March–June 2024)
Acinetobacter baumannii
Klebsiella pneumoniae
Pseudomonas aeruginosa
Escherichia coli
Number of Isolates
20
30
40
50
60
March
April
May
June
Months (2024)

Discussion

The rising prevalence of multidrug-resistant Gram-negative bacteria (MDR GNB) poses a major threat to healthcare systems, leading to increased morbidity and mortality due to limited treatment options[7,8]. Recognizing patients at high risk for MDR GNB is crucial for timely interventions and improved patient outcomes[9]. Our study identified prior antibiotic use, ICU admission, and the presence of indwelling medical devices as the most significant risk factors for MDR GNB acquisition, aligning with findings from previous research. Adopting global recommendations, particularly those from the WHO, can help in the early detection of colonized or infected patients through targeted screening of high-risk individuals. This approach will be instrumental in curbing the spread of MDR pathogens by implementing evidence-based[20] infection control strategies. Several international studies support our findings. Kalam et al. (2014) examined risk factors for carbapenem-resistant GNB bacteremia in adults and highlighted age above 50, septic shock, prolonged ICU stay, and immunosuppressive therapy[11] as key contributors. Similarly, research in Iran by Mohsenpour et al. (2016) associated ICU admission, prior antibiotic exposure, and central venous catheterization with imipenem-resistant[12] GNB infections. Ting et al. found that prior use of carbapenems, cephalosporins, and anti-pseudomonal penicillins, along with prolonged hospitalization, significantly increased the likelihood of acquiring carbapenem-resistant GNB[13].Data from Saudi Arabia[17] also reinforce these risk factors. Al-Otaibi et al. (2016) studied bacteremia caused by MDR GNB in an oncology center and found ICU admission, prior surgery, and central line insertion as primary risks. Another study by Al Hamdan et al. (2022) observed that MDR GNB[14] were more common in female patients and those aged 20-29 years[15], with mechanical ventilation for more than three days[16] being a key risk factor.In our study, A. baumannii and K. pneumoniae were the predominant MDR organisms, surpassing P. aeruginosa and E. coli. Patients with MDR infections were more likely to have a history of antibiotic use, ICU admission, and invasive medical devices. On the other hand, those infected with non-MDR organisms were more commonly affected by prolonged hospital stays, immunosuppression, and older age.To combat the rising threat of MDR GNB in Pakistan, there is an urgent need for enhanced antimicrobial stewardship programs, stricter infection control measures, and improved ICU protocols to prevent transmission. Implementing WHO guidelines in local healthcare settings will provide an added layer of protection against MDR infections. By integrating global best practices with context-specific interventions, we can work towards reducing the burden of MDR GNB and improving patient outcomes in our hospitals.

Conclusion

The factors contributing to the emergence of multidrug-resistant Gram-negative bacteria (MDR GNB) have not been extensively explored in Pakistan. Our findings highlighted that *A. baumannii* (38%) and *K. pneumoniae* (31%) were the most frequently isolated MDR pathogens. We also identified key risk factors such as previous antibiotic use, prolonged ICU stays, and the presence of indwelling medical devices as the primary contributors to MDR GNB infections. These findings underscore the need for robust surveillance systems and the implementation of effective antibiotic stewardship programs to help curb the spread of MDR bacteria in healthcare settings. By focusing on these preventive measures, we can mitigate the growing threat of MDR GNB and improve patient care outcomes.

Additional Information

Author Contributions.

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Drafting of the manuscript: Kashif khan[8], Umair khan[9],Ahmad Zeb[10] Shaheer Ahmad Dar[6], Sadeed Ahmed[7]

Critical review; Hina Gulzar[1], Aizaz Ur Rahman[2],Taiseem Aslam[3] Bilal Hassan[5]

Disclosures
Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.

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8. Risk Factors for the Spread of Antibiotic-Resistant Bacteria https://link.springer.com/article/10.2165/00003495-199855030-00001
9. Tumbarello et al. (2015) conducted a multicenter study to analyze variations in treatment and mortality outcomes among patients infected with Klebsiella pneumoniae carbapenemase (KPC)-producing *Klebsiella pneumoniae*, emphasizing the challenges in managing these infections.
10. Capone et al. (2013) highlighted the high prevalence of colistin resistance in patients with carbapenem-resistant *K. pneumoniae* infections, linking it to increased mortality rates and limited treatment options.
11. Giacobbe et al. (2015) performed a multicenter case-control study to determine risk factors associated with bloodstream infections caused by colistin-resistant KPC-producing *K. pneumoniae*, identifying prior antibiotic exposure and ICU stays as significant contributors.
12. The World Health Organization (WHO) released an implementation manual in 2019, providing guidelines for preventing and controlling the spread of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* at both national and healthcare facility levels.

13. Kalam et al. (2014) examined risk factors for carbapenem-resistant Gram-negative bacteremia in a developing country, identifying prolonged hospital stays, ICU admissions, recent antibiotic use, and mechanical ventilation as key determinants of infection.
14. Mohsenpour et al. (2016) investigated imipenem resistance in Gram-negative bacterial isolates from Iranian hospitals, reporting that previous exposure to broad-spectrum antibiotics, invasive procedures, and prolonged hospital admissions were significant risk factors.
15. Ting et al. (2018) conducted a retrospective case-control study on carbapenem-resistant Gram-negative bloodstream infections, finding that prolonged use of carbapenems and anti-pseudomonal agents, as well as hospitalization exceeding two weeks, significantly increased infection risk.
16. Al-Otaibi et al. (2016) studied bloodstream infections in oncology patients, demonstrating that multidrug-resistant *E. coli*, *A. baumannii*, and *Pseudomonas spp.* were the leading pathogens, with central venous catheters, chemotherapy-induced neutropenia, and ICU admissions being major risk factors.
17. Al Hamdan et al. (2022) analyzed multidrug-resistant Gram-negative bacteria in Eastern Saudi Arabia, reporting an alarming rise in antimicrobial resistance. Their study emphasized that mechanical ventilation for more than three days, female gender, and younger age groups were associated with higher rates of infection.