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Epidemiology of MDR Infections in the ICU: Comparing Outcomes in Patients with and Without Prior Antibiotic Exposure

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ABSTRACT

Background: The significant challenge in Intensive Care Units (ICUs) are so-called multidrug-resistant (MDR) infections, which can cause higher morbidity, longer hospitals stays and high emission costs. The impact of prior antibiotic exposure as a risk factor of the development of MDR organisms is widely recognized but patient outcome is still controversial.

Objective: The trial was designed to compare the clinical outcomes of patients with MDR infection in the ICU according to the history of previous exposure to antibiotics.

Methods: The study was an observational study conducted over a period of 8 months; January-August 2023, in Medical, and Surgical ICU units of Mayo Hospital, Lahore. Three hundred and twenty patient developing culture-confirmed MDR infections 48 hours or later of ICU admission were included. They categorized patients into two groups depending on recorded system antibiotics utilization within 90 days prior ICU. Clinical/demographic parameters have been examined and multivariate logistic regression was done to assess independent predictors of mortality.

Result: A total of 176/320 (55.0%) patients had the history of previous antibiotic exposure. The incidences of diabetes (48.9% vs. 36.1%, p=.3, CKD (35.2% vs. 24.3%, p=.2, thrombocytopenia (30.7%vs.18.8%, p=0.01) and prolonged ICU stay (10 vs. 7 days, p=4) were high among these patients. Yet, the previous exposure to antibiotics was not an independent predictor of death (OR=110p=058). Rather, lengthy mechanical ventilation, prolonged ICU stay and indwelling lines were substantial predictors.

Conclusion: While prior antibiotic exposure is associated with increased morbidity and longer hospital stays, it does not independently increase mortality risk in ICU patients with MDR infections.

Keywords: *infections, ICU outcomes, prior antibiotic exposure, antimicrobial resistance, patient mortality*

1. INTRODUCTION

Multidrug resistance (MDR) infection is an emerging issue of public health importance especially in the intensive care units (ICUs), as the patients are at extreme risk by being hospitalized and having severe illness, invasive procedures, and long stays (Fernz-Martinez et al., 2022;Schinas et al., 2023). MDR pathogens cause a vast level of morbidity, lengthy stays, and higher hospital expenditures and are also a major contributor to the worldwide burden related to hospital-acquired infections

(Assefa & Amare, 2022; Teng et al., 2023). It is well-established that the formation of resistance strictly depends on the course of antibiotics use, and previous exposure to antimicrobials is identified as a critical risk factor in the onset of MDR infections (Xi et al., 2022; Muteeb et al.,2023). The study aims to investigate the epidemiology and prognoses of MDR infections in ICU patients,their relationship to exposure to prior antibiotics.

The issue of antimicrobial resistance (AMR) is aided in low- and middle-income countries like Pakistan by the overuse and abuse of antibiotics, inadequate activities concerning infection control,and the lack of effective antimicrobial stewardship programs (Sulis, Sayood,& Gandra, 2022;Rony, Sharmi, & Alamgir, 2023). ICU conditions are especially prone to the spread of MDR organisms, as broad-spectrum antibiotics are routinely used, as are invasive devices, and patients have low immunity (Fatima, Purkait, Rehman, Rai, & Hameed, 2023; Catalano et al., 2022).The key consideration in the development of tailored interventions reducing both patient outcomes and the propagation of resistance is the identification of patients at risk of developing MDR infections,as well as the clinical implications of antibiotic exposure before the ICU admission (Bassetti,Tschudin-Sutter,Egli,&Osthoff,2022;Kalin,Alp, Chouaikhi, & Roger,2023).

Prior studies have also pointed out the connection of prior antibiotic exposure with enhanced risk of infection by MDR pathogens like Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa (Roy et al., 2022; Assefa, 2022). Such organisms tend to be resistant to many classes of antibiotics, significantly narrowing the treatment choices, so that agents of last resort must be considered, such as colistin or tigecycline, but these are also relatvely toxic and not highly effective in their own right (Abushanab, Nasr, & Al-Badriyeh, 2022; Adeniji, Nontongana,Okoh, & Okoh, 2022). Whether prior use of antibiotics is a predictive risk factor of mortality in the ICU is however unclear, though it is a proven risk factor on the development of resistance.Alternatively, some literature indicates that, although exposure to antibiotics has been linked to colonisation or infection with resistant bacteria, it does not, in isolation, increase mortality, when adjusted by other factors such as the severity associated with the condition, comorbidities,and the interventions used in Intensive Care Units (Ceccarelli et al., 2022; Alnimr, 2023).

This observational study took place in ICUs of Mayo Hospital, Lahore, and 320 cases of patients who acquired culture-confirmed MDR infections 48 hours after ICU admission were included.This factor was used to categorize the patients into two groups of patients with and without a recent exposure to antibiotics in the 90 days before ICU hospitalization to establish whether it altered clinical characteristics and patient outcome, especially their mortality. The reason to choose a 90-day window lies in the current literature that suggests that the recent exposure to antibiotics is a major risk factor of MDR colonization and infection.

In evaluating this association, researchers adjusted these confounding variables that included; age,gender,comorbidities (including diabetes, chronic kidney disease and liver disease), length of ICU stay and use of invasive devices. Multivariate analysis facilitated identification of independent predictors of mortality providing clearer picture of the value of prior antibiotic exposure in the setting of overall ICU morbidity and mortality.

This study is relevant not only in enhancing the local epidemiological interpretation of MDR infections but also due to its implication on antibiotic stewardship and management of ICUs. When it is observed that prior antibiotic use was a factor that put patients at a high healthcare use-longer ICU stays,longer mechanical ventilation, and frequent complications, early identification of such patients can serve as a guideline in resource allocation and clinical decision-making. Moreover, in the absence of antibiotic exposure as an independent variable increasing mortality, one might reconsider the risk stratification in critically ill patients, the prioritization of interventions.

This study, in short, contributes to the already-available body of evidence,which points to the association between exposure to antibiotics and the risk of developing MDR infection but investigates whether this association translates to more disadvantageous clinical results. It would provide guidance to improved practices in the management of ICUs, antimicrobial stewardship and infection prevention eventually helping make progress towards reducing the consequences of MDR pathogens in intensive care units. Due to the identification of alterable risk factors and the elucidation of their impact on patient outcome, the study supports the significance of individualised strategies in the battle against AMR in ICUs.

2. METHODOLOGY

This is a single-center observational study that was performed in the Medical and Surgical Intensive Care Units (ICUs) of Mayo Hospital, Lahore, in 8 months during the period January 2023-August 2023. The study included a population of 320 patients with multi-drug resistant (MDR) infections and developed it at least 48 hours after their stay in ICU. Purposive sampling was applied to the selection of patients that were identified according to specific inclusion and exclusion criteria. Inclusion criteria were those patients aged 18 years or more, admitted at the Medical ICU or Surgical ICU during the study time, and developed culture-proven MDR infection at least 48 hours after admission to the ICU. Patients with MDR infection at hospital admission,patients with ICU shorter than 48 hours and patients with incomplete medical records were excluded.

Electronic medical records and patient charts were used to collect clinical and demographical data.The variables collected were age, gender, comorbidities (e.g.,diabetes mellitus, chronic kidney disease, decompensated chronic liver disease, and cerebrovascular accidents), hospitalization during the previous six months, the use of antibiotics during the previous 90 days,

prior to ICU admission. Length of ICU stay and hospital stay, mechanical ventilation time, presence of central venous lines and urinary catheters and thrombocytopenia were also documented as ICU related factors.

The patients were divided into two categories according to the previous antibiotics exposure: The first one included patients who were exposed to systemic antibiotics within 90 days preceding ICU admission, and the second one included patients who had not been exposed to antibiotics before admission. IBM SPSS Statistics (version XX) was used to analyse the data. Thend the Kolmogorov was used to test the normality of continuous variables. The comparison of categorical variables was quantified using the Chi-square test and continuous using the Mann-Whitney U test.Multivariate Logistics regression analysis was used to find out the independent predictors of mortality in patients with MDR infections. A p value lower than 0.05 would be accepted as a statistical significance.

Ethical Considerations

No direct interventions were performed, and informed consent was waived due to the observational nature of the study.

3. RESULTS

A total of 320 patients who developed culture-confirmed multidrug-resistant (MDR) infections 48 hours after ICU admission were included in this study. The mean age was 60.2±15.1 years, with 173 (54.2%) patients under 65 years and 147 (45.8%) aged 65 years and above. Of the total,162 patients (50.7%) were male. Among comorbid conditions, 138 patients (43.1%) had diabetes mellitus, 97 (30.3%) had chronic kidney disease (CKD), 75(23.4%) had decompensated chronic liver disease (DCLD), and 62 (19.4%) had cerebrovascular accidents (CVA). A total of 104 patients (32.5%) had a documented hospitalization within the past six months, while 176 patients (55.0%) had received systemic antibiotics within the 90 days preceding their ICU admission (Table 1).

Table 1.Demographic and Clinical Characteristics of Patients(n=320)

Variable	$\boldsymbol{Overall(n = 320)}$
Age(mean±SD)	60.2 ± 15.1
$Age < 65$years	173(54.2%)
$Age \geq 65 years$	147(45.8%)
Gender (Male)	162(50.7%)
Diabetes Mellitus	138(43.1%)
Chronic Kidney Disease (CKD)	97(30.3%)
Decompensated Chronic Liver Disease (DCLD)	75(23.4%)
Cerebrovascular Accident (CVA)	62(19.4%)
Hospitalization in Last 6 Months	104(32.5%)
Prior Antibiotic Use	176(55.0%)

Comparison Between Patients With and Without Prior Antibiotic Exposure

As shown in Table 2, notable variation arose between the distribution of clinical characteristics and outcomes between exposed and naive patients. There was a higher probability of male (57.4% vs.49.33%,p=012)and diabetic patients having a history of prior antibiotic use (48.9%VS.336.1.1%,p=0.03). In the same way, the prevalence of CKD was higher in previously exposed people to antibiotics (35.2%、VS.24.3%,p=0.02).Due to less occurrence of DCLD and CVA in antibiotic treatment group, the results were not statistically significant.

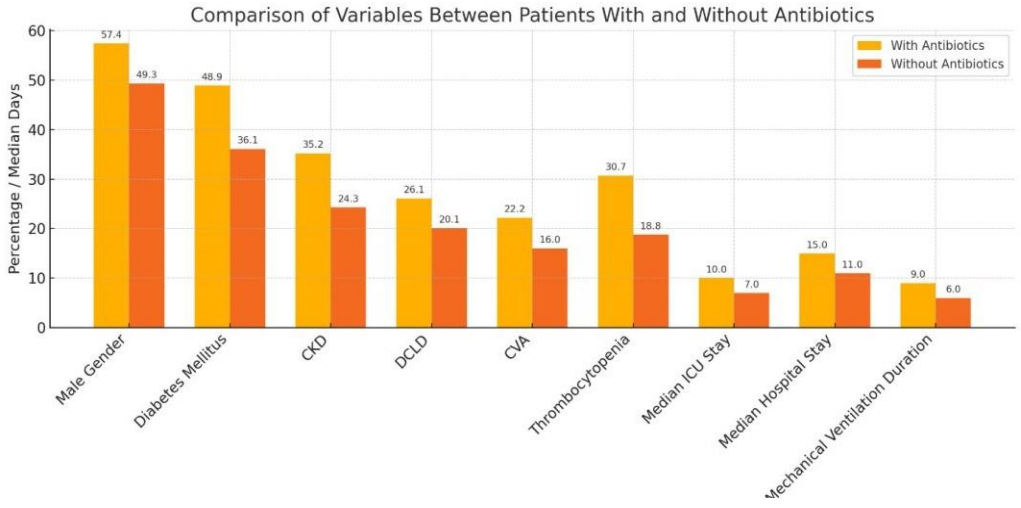
MDR infections and critical illness: Thrombocytopenia, which is an important complication of these values was detected much more frequently in the antibiotic group (30.7%vs.18.8%,p=0.01).

In addition, ICU stay (median 10 vs. 7 days,p=0.004)as well as hospital stay (median 15 vs.11days,p=0.005) and mechanical ventilation (median 9 vs. 6 days,p=0.007)were all significantly longer in patients who received prior antibiotics.

Table 2. Comparison Between Patients With and Without Prior Antibiotic Exposure

Variable	With Antibiotics ($n = 176$)	Without Antibiotics ($n = 144$)	p-value
Number of Patients	176	144	-
Male Gender	101(57.4%)	71(49.3%)	0.12
Diabetes Mellitus	86(48.9%)	52(36.1%)	0.03
CKD	62(35.2%)	35(24.3%)	0.02
DCLD	46(26.1%)	29(20.1%)	0.21
CVA	39(22.2%)	23(16.0%)	0.27
Thrombocytopenia	54(30.7%)	27(18.8%)	0.01
Median ICU Stay (days)	10	7	0.004
Median Hospital Stay (days)	15	11	0.005
Mechanical Ventilation (median duration,days)	9	6	0.007

Figure:1



Predictors of Mortality

Multivariate logistic regression analysis was used to evaluate mortality independent predictors.Results demonstrated that prolonged mechancal ventilation(OR=2.14,95%CI:1.523.01,p<0.001),extended ICU stays(OR=.85,95%CI:1.302.63,p<0.001),,and use of indwelling lines p<0.001)were strongly related to higher Interestingly,there was (OR=1.92,95%CI:1.362.70no significant impact of previous exposure to antibiotics on mortality(OR=1.1095% CI:0.78;1.55,p=0.58)and suggests that despite the known correlation between antibiotic use and prolonged hospital and ICU length of stays, antibiotics alone did not result in an increase of the risk of mortality.

Table 3. Multivariate Logistic Regression Analysis of Factors Associated with Mortality

Variable	Odds Ratio (OR)	95% CI	p-value
Duration of Mechanical Ventilation	2.14	1.52-3.01	<0.001
Length of ICU Stay	1.85	1.30-2.63	<0.001

Use of Indwelling Lines	1.92	1.36-2.70	<0.001
Prior Antibiotic Use	1.10	0.78-1.55	0.58

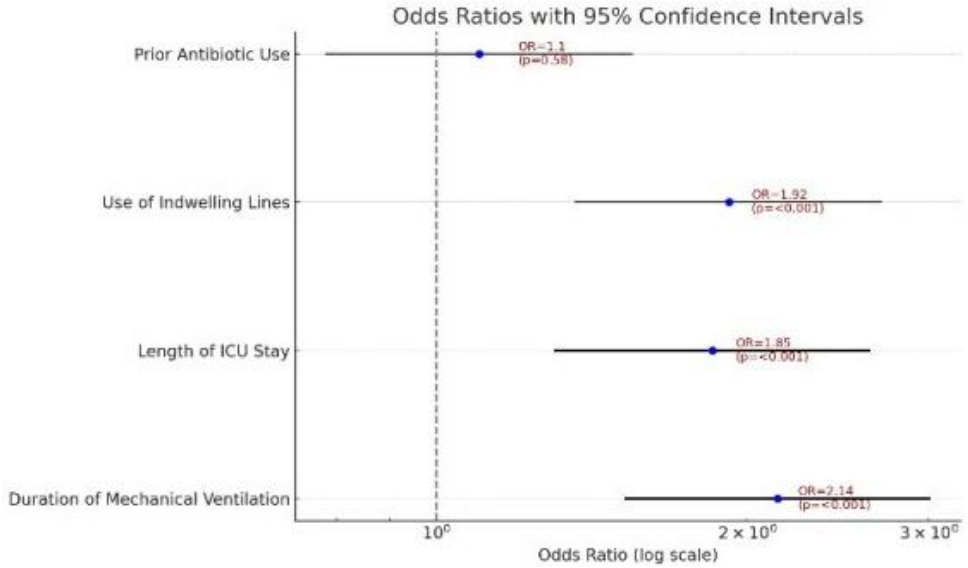


Figure:2

Summary of Key Findings

Patients with comorbidity such as diabetes and CKD were significantly more prevalent in patients previously exposed to antibiotics.

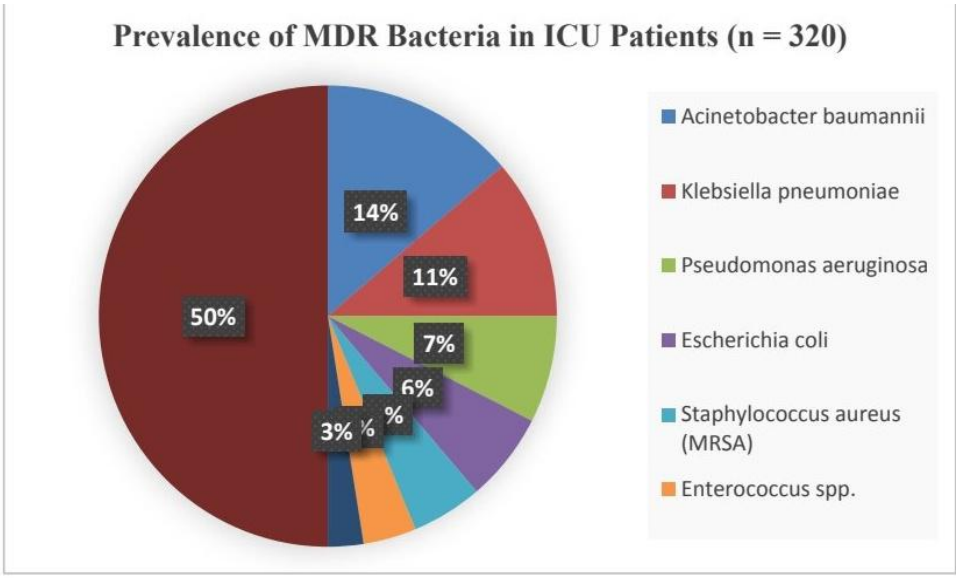
They were also more likely to experience thrombocytopenia with marked ICU and hospital stay.

The length of mechanical ventilation was also significantly greater in the group exposed to antibiotics.

Although clinical parameters were worse and hospital stays were longer, mortality rates were not significantly different in both groups.

Exposure to antibiotics was not an independent prognostic factor of mortality, whereas prolonged ventilation, extended ICU stay duration, and utilization of indwelling lines were significant predictor factors.

Figure: 2



4. DISCUSSION

The results of this investigation give important implications towards the epidemiology and clinical consequences of multidrug-resistant (MDR) infections in ICU patients, specifically median outcomes of MDR versus non-MDR infections in prior antibiotic exposure. These findings demonstrate the multifactorial situation of morbidity and mortality related MDR infection in critically ill patients and pose critical questions about antibiotic stewardship and ICU practices.

We found that over fifty percent of the MDR infected patients admitted to the ICU have a history of systemic antibiotics use in the last 90 days. This is in tandem with the available literature, which has echoed several times that previous exposure to antibiotics has been a major risk factor in the causes of MDR pathogens. Pre-existing antibiotic exposes the patient to microbiota that are possibly altered by previous use and puts a selective pressure allowing resistance to develop.Nevertheless, even though the prevalence of comorbidities and the clinical burden tended to be greater in these patients compared with patients withoutprior antibiotic exposure, including diabetes mellitus, chronic kidney disease, prior antibiotic exposure was not an independent mortality predictor in our multivariate model.

This observation corresponds to numerous other studies, who despite reporting the existence of a relationship between antibiotic exposure and the development of MDR, failed to show a direct association with higher mortality. Rather,we found the duration of mechanical ventilation, length of ICU stay, and the use indwelling lines to be independent predictors of mortality in our data which were other ICU-related factors. These findings underscore the significance of an ICU-related practices on outcomes of critically ill patients. Though invasive procedures are sometimes unavoidable, they can make the patients susceptible to secondary infections and have contributed to poor outcomes unless managed in the best way possible.

The fact that patients who had previous exposure to antibiotics had significantly longer stays in the ICU and hospital should serve as reminders on the extra burden that these patients encounter within healthcare systems. It proposes an antecedent-consequent loop in which previous administration of antibiotics leads to the MDR infection that, in turn, requires further treatment involving stronger and more lengthy medications, leading to growing healthcare expenses as well as the development of new infections and complications. Despite not being significantly different,mortality rates show a higher utilization of resources by the antibiotic-exposed group, which would be of clinical and economic importance.

Thrombocytopenia was also significantly more prevalent in the antibiotic exposure population and can be indicative of a more illness or secondary consequences due to infection as well as antibiotic treatment. Though the diagnosis of thrombocytopenia did not independently predict mortality in this case, it is commonly linked with poor outcomes in critically-ill patients; it can be considered a proxy measure of the severity of a critical illness or sepsis.

Analysis of the results must also lead to consideration of patterns of administering antibiotics,especially in outpatient and inpatient practices prior to the admission to ICU. Antimicrobial stewardship activities should strive to promote rational use of antibiotics since early and inappropriate prescription can be the culprit in the development of complications in the fu during critical care. The risk of MDR emergence may be curbed by judicious use antibiotics,and quick de-escalation plans depending on culture findings, which may potentially eliminate extra exposures to the broad-spectrum therapy.

Though this study deserves some strengths, such as a fairly big sample size and a strong multivariate analysis, it cannot remain without a number of limitations. It is limited as a single-center observational study and the results cannot be applied to other facilities that have diverse patient populations, microbial ecology and antibiotic stewardship initiatives. Also residual confounding dissimilar to the measured variables including severity of illness (e.g. APACHE II or SOFA), nutritional status, and microbiological profile are at dearth significant opportunities.

5. CONCLUSION

To sum up, this study emphasises that although prior exposure to antibiotics affects morbidity and resource use in ICU patients with MDR infections, it is not independently associated with mortality. Rather, more important outcome determinants are ICU related factors, including mechanical ventilation, long stay in the ICU, and the use of invasive lines. The results justify the maintenance of rigorous infection prevention policies, close surveillance of the ICU practice, and effective antimicrobial stewardship initiatives to control and lessen the burden of MDR infections in the critical care arena.

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