Clinical and Economic Burden of Multidrug-Resistant Infections in Critically Ill Patients: Impact On ICU Mortality, Length of Stay, and Healthcare Resource Utilization—A Prospective Observational Study

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Received on: 17 August 2026; Accepted on: 04 September 2026; Published on: 15 October 2026

ABSTRACT

Background: Multidrug resistance (MDR) has become a significant problem in intensive care units (ICUs), where it results in mortality, longer hospital stays and unnecessary use of health care resources. The goal of this study was to assess the effects of MDR infections on clinical outcomes and/resources utilization in critically ill patients.

Materials and methods: A prospective observational study of 300 adult-ICU patients with microbiologically confirmed bacterial infection were performed. Patients were classified into two groups, MDR (n=118) and non-MDR (n=182) groups, according to ASB. Demographic and clinical parameters, microbiological results, utilization of health services and clinical outcomes were documented. Multivariable logistic regression analysis was carried out to determine independent predictors of ICU mortality.

Results: MDR infections were detected in 39.3% of patients. The most frequently reported infection source was ventilator-associated pneumonia (VAP), and MDR pathogen species most often reported was carbapenem-resistant Acinetobacter baumannii. The mortality rate at ICU was significantly higher for MDR infections than non-MDR infections (41.5% vs 19.8%, $p<0.001$). MDR-infected patients also experienced higher rates of septic shock (45.8% vs. 24.2%), acute kidney injury (39.8% vs. 23.6%), mechanical ventilation (77.1% vs. 56.6%), and vasopressor use (70.3% vs. 48.9%) (all $p<0.05$). The population of the MDR group was significantly associated with greater healthcare resource use such as longer days in the ICU (15.4±8.1 vs. 8.7±5.2 days, $p<0.001$); longer hospitalisation; higher antibiotic use, and higher treatment costs (all $p<0.001$). MDR infection was an independent risk factor for ICU mortality (adjusted OR 2.84, 95% CI 1.67–4.82, $p<0.001$) in multivariable analyses.

Conclusion: MDR infections make the clinical outcome of critically ill more severe and the use of healthcare resources more expensive. Improved antimicrobial stewardship, infection prevention, and prompt early pathogen-directed therapy can counter the trend of increasing numbers of MDR infections in ICUs.

Keywords: Multidrug-resistant infections, Intensive care unit, ICU mortality, Antimicrobial resistance, Healthcare resource utilization, Length of stay, Critical care, Carbapenem resistance.

INTRODUCTION

Antimicrobial resistance (AMR) is a growing threat to global health that threatens the effectiveness of available antimicrobials and contributes to global morbidity, mortality and health care costs. In 2019, it was estimated that antimicrobial-resistant infections resulted in almost 4.95 million deaths worldwide,[1] making it a big problem today. Patients in the hospital are especially susceptible to multidrug-resistant (MDR) infections due to various factors, including critical illness, length of stay, invasive procedures, prior antibiotic treatments, mechanical ventilation and compromised immunity.[2]

Infections caused by multidrug-resistant organisms (MDROs), such as methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Enterobacterales (CRE), multidrug-resistant Pseudomonas aeruginosa (MDR-Pae), and vancomycin-resistant enterococci (VRE), have become more common in critical care units around the world.[2,3]

The new appearance of these pathogens, and the fact that they can spread to other farms, have made infection control difficult, as there are less therapeutic choices and risk of failure. A number of studies have shown that adverse clinical outcomes are linked to the occurrence of MDR infections. In a large multicenter study conducted in India, death risk was significantly higher for infections with MDR and XDR pathogens than in susceptible infections especially in patients admitted to the intensive care unit (ICU) who had Gram-negative pathogen. A large multicenter study conducted in India observed that mortality was significantly higher for MDR and XDR pathogens than in susceptible infection, especially for patients admitted to the intensive care unit (ICU) with infection with a Gram-negative pathogen.[4]

Likewise, systematic reviews have indicated that MDR HCIs in ICUs also are associated with higher mortality, higher hospital costs, and higher clinical complexity in cases of Acinetobacter baumannii and of carbapenem-resistant Gram-negative bacteria.[3,5]

In addition to clinical impacts, MDR infections have a significant economic impact on the healthcare system. Problems with antimicrobial treatments, repeated microbiological troubleshooting, longer mechanical ventilation and longer stay on the ICU are related to resistant infections. A population-based study revealed that MDR bacterial infections significantly contributed to hospital mortality, hospital stays and burden of disease

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How to cite this article: Singh S, Singh V. Clinical and Economic Burden of Multidrug-Resistant Infections in Critically Ill Patients: Impact on ICU Mortality, Length of Stay, and Healthcare Resource Utilization—A Prospective Observational Study. Adv. Med. Res. Pract. 2026;1(1):3-7. https://doi.org/10.21276/amrp.2026.v1.i1.2
Source of support: Nil
Conflict of interest: Non

costs, with an estimated of billions of dollars in additional healthcare costs each year.[6] In a resource limited healthcare system with scarce number of ICUs, the use of such facilities is especially related. Although there has been an increase in the awareness of AMR, there is a limited number of prospective data to assess the effect of MDR infections on mortality and/or length of stay in intensive care together with the use of healthcare resources, especially in LMIC countries where the impact of AMR is disproportionately high.[4] Additionally, country specific distribution of pathogens, antibiotic usage and antimicrobial management patterns require individual evaluation of each institution for appropriate antimicrobial stewardship and allocation policies. In light of this, it became important in the present study to analyze the effect of MDRO infections on the mortality, duration of stay in the ICU, and use of health care resources of critically ill individuals. A grasp over the clinical and economic consequences of MDR infections might help in the development of evidence-based interventions, to reduce the burden of antimicrobial resistance and to improve outcomes in intensive care setting.

Materials And Methods

Study Design and participants

Prospective observational study conducted in the Intensive Care Unit (ICU) of a complex tertiary care teaching hospital for 18 months following approval by the Indian council for Medical Research Ethics committee of the hospital. Patients were screened for inclusion if they were an adult (≥18 years) admitted to the ICU who became microbiologically confirmed to have a bacterial infection during their stay in the ICU. Patients were excluded if they had incomplete clinical information, if their intensive care unit (ICU) length of stay was less than 24 hours, if they had fungal infection only, viral infection only or if they were transferred from other institutions with initial ongoing multidrug-resistant (MDR) infections.

Data collection and Definitions

A Data prospectively were recorded by using standard case record form including the demographic characteristics, comorbidities, severity of illness, infection site, finding of microbiology, antimicrobial susceptibility patterns, treatment details, and clinical outcomes. On the basis of international consensus, MDR infection was classified as resistance to three or more agents from three or more antibiotic classes. Patients were classified as either MDR and non-MDR infection group for comparison.

Outcome measures

The primary outcome was death in ICU. Secondary outcomes were duration of mechanical ventilation, duration in the ICU (intensive care unit), use of anti-microbials, requirement for organ support and healthcare resource utilization. The drug use rates, the rate of diagnostics, the rate of invasive procedures and the rate of the ICU beds were used to assess their resource use.

Statistical Analysis

SPSS version 26.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables were presented as Mean ± SD or Median (IQR) and categorical variables were presented as Frequencies and Percentages. The independent t-test, Mann Whitney U-test or Chi-square test/Fisher's exact test were used for comparisons between groups for continuous variables and categorical variables respectively. Using multivariable logistic regression, significant variables that were associated with the death in the ICU were identified. The statistical significance was based on p values <0.05.

Results

The study enrolled a total of 300 patients who had been diagnosed microbiologically with bacterial infections and were extremely sick. Of these, 118 (39.3%) had infections due to multidrug resistant (MDR) organisms, and 182 (60.7%) had infections due to non-MDR organisms. The overall ICU mortality rate was 28.3% (85/300).

For baseline demographic and clinical features between MDR and non-MDR bacteria, see [Table 1]. APACHE II and SOFA scores were significantly higher, and a higher prevalence of chronic kidney disease at admission were noted for patients in the MDR group, reflecting a higher severity of illness when admitted to the ICU. [Table 2] reports the distribution of infections sites and MDR microorganisms in relation to the affected patients. Ventilator-associated pneumonia (VAP) was the most frequent infection source, and carbapenem-resistant Acinetobacter baumannii (CARB) became the main pathogen that had developed MDR. The clinical outcomes by MDR status are summarized in [Table 3]. For patients with MDR infections, the mortality in the ICU, septic shock, acute kidney injury, mechanical ventilation and the use of vasopressors were significantly higher than for patients with non-MDR infections. The results of the analysis of healthcare resource utilization for the study groups are presented in [Table 4].

The median duration of the ICU stay and hospital stay, as well as the duration of mechanical ventilation, antibiotic usage, and treatment costs, were significantly higher for MDR infections. The multivariable logistic regression analysis of the predictors of ICU mortality is presented in [Table 5].

Additionally, MDR infection was an independent predictor for mortality after adjusting for potentially confounding variables, even in the presence of APACHE II score, septic shock, mechanical ventilation, and chronic kidney disease.

The monthly number of MDR infections is presented in [Figure 1] for the study period. An increase in MDR is noted from January to August, while a slight decrease is noted towards the end of the year to the end of December. Resistance levels of MDR isolates are shown in [Figure 2] for the major antimicrobial classes. The highest resistance rate was seen with cephalosporins and carbapenems, while the lowest resistance rate was seen with colistin. The relationship between time to initiation of suitable antibiotic therapy and ICU mortality is shown in [Figure 3].

It appears that treatment lag was highly associated with mortality and the latter went up incrementally with treatment delay, with a 48-hour delay associated with the

highest mortality among those patients who were treated appropriately.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	MDR (n=118)	Non-MDR (n=182)	p-value
Age (years)	59.8 ± 15.1	57.6 ± 14.7	0.214
Male sex, n (%)	73 (61.9)	108 (59.3)	0.657
Diabetes mellitus, n (%)	51 (43.2)	63 (34.6)	0.132
Hypertension, n (%)	48 (40.7)	67 (36.8)	0.497
Chronic kidney disease, n (%)	24 (20.3)	21 (11.5)	0.038
COPD, n (%)	19 (16.1)	22 (12.1)	0.318
APACHE II score	22.8 ± 6.4	18.7 ± 5.8	<0.001
SOFA score	9.6 ± 3.1	7.2 ± 2.8	<0.001

Patients with MDR infections had significantly higher APACHE II and SOFA scores, indicating greater baseline disease severity.

Table 2: Distribution of Infection Sites and MDR Pathogens

Variable	n (%)
Ventilator-associated pneumonia	47 (39.8)
Bloodstream infection	28 (23.7)
Catheter-associated UTI	21 (17.8)
Intra-abdominal infection	13 (11.0)
Surgical site infection	9 (7.6)
Carbapenem-resistant Acinetobacter baumannii	41 (34.7)
ESBL-producing Klebsiella pneumoniae	29 (24.6)
MDR Pseudomonas aeruginosa	22 (18.6)
Carbapenem-resistant Enterobacterales	16 (13.6)
MRSA	10 (8.5)

Table 3: Clinical Outcomes According to MDR Status

Outcome	MDR (n=118)	Non-MDR (n=182)	p-value
ICU mortality, n (%)	49 (41.5)	36 (19.8)	<0.001
Septic shock, n (%)	54 (45.8)	44 (24.2)	<0.001
Acute kidney injury, n (%)	47 (39.8)	43 (23.6)	0.003
Mechanical ventilation, n (%)	91 (77.1)	103 (56.6)	<0.001
Vasopressor requirement, n (%)	83 (70.3)	89 (48.9)	<0.001
Tracheostomy, n (%)	28 (23.7)	17 (9.3)	0.001

Table 4: Healthcare Resource Utilization

Parameter	MDR	Non-MDR	p-value
ICU stay (days)	15.4 ± 8.1	8.7 ± 5.2	<0.001
Hospital stay (days)	24.1 ± 10.3	14.8 ± 7.4	<0.001
Mechanical ventilation duration (days)	10.2 ± 6.7	5.1 ± 3.9	<0.001
Number of antibiotics used	4.2 ± 1.5	2.3 ± 1.1	<0.001
Diagnostic cultures per patient	5.8 ± 2.1	3.4 ± 1.6	<0.001
Total treatment cost (USD)	8,960 ± 2,340	4,870 ± 1,620	<0.001

Table 5: Multivariable Logistic Regression for ICU Mortality

Variable	Adjusted OR	95% CI	p-value
MDR infection	2.84	1.67–4.82	<0.001
APACHE II score	1.11	1.05–1.18	<0.001
Septic shock	2.36	1.38–4.04	0.002
Mechanical ventilation	1.91	1.09–3.37	0.024
Chronic kidney disease	1.74	1.01–3.01	0.047

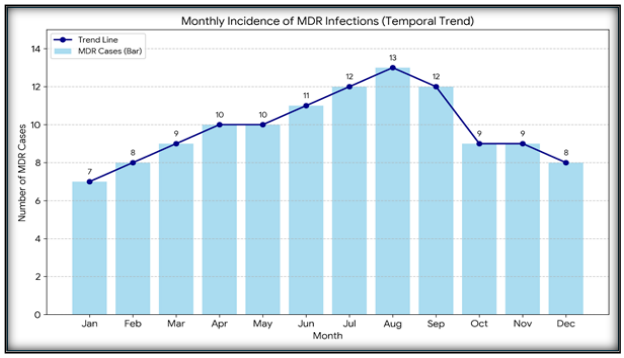


Figure 1: Monthly Incidence of MDR Infections

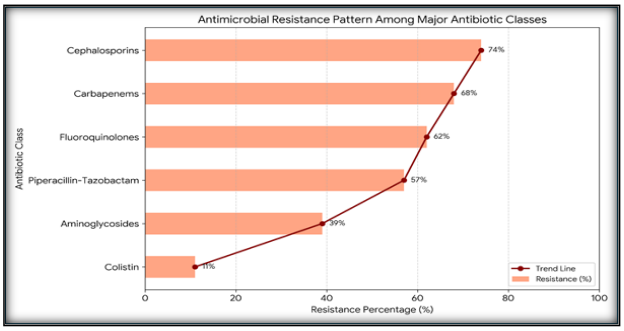


Figure 2: Antimicrobial Resistance Pattern Among Major Antibiotic Classes

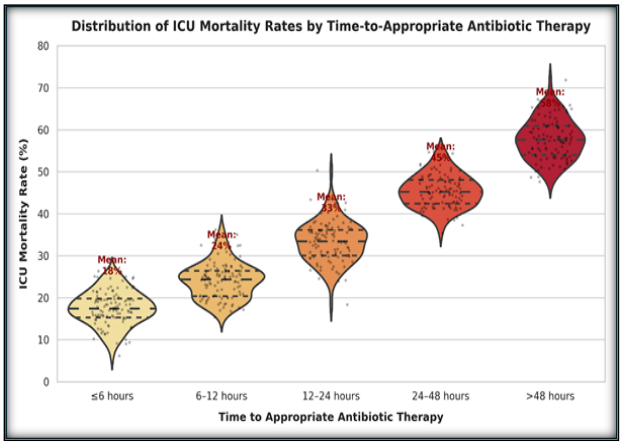


Figure 3: ICU Mortality According to Time-to-Appropriate Antibiotic Therapy

DISCUSSION

The present prospective observational study showed that multidrug-resistant (MDR) infections resulted in significantly longer hospital stays, more hospitalization morbidity events, more organ support and significantly higher healthcare resource utilization in the intensive care unit (ICU), as well as a significantly increased mortality rate. In a multivariable logistic regression model adjusted for additional clinical and demographic variables, the mortality risk associated with MDR infection remained an independent predictor of ICU mortality as the multivariate group with MDR infections had a mortality rate of 41.5% versus 19.8% for the non-MDR multivariate group (aOR: 2.84, 95% CI: 1.67–4.82). The results are supportive of the emerging data that antimicrobial resistance is an important driver of poor clinical and cost outcomes in patients experiencing critical illness.

The dominance of Gram-negative MDR pathogens found in the present study, especially of CPE such as Acinetobacter baumannii and ESBL-producing Klebsiella pneünmoniae, corroborate with the observations made in intensive care ward in the recent times. In India Gautam et al,[3] reported a high incidence of antimicrobial resistance in Gram-negatives as majority of resistant infections occurred in ICU. As observed above, resistant Gram-negative bacteria are still a major problem in the critical care setting, similar to Uluç et al,[2] who found MDR and the presence of extensively drug resistant pathogens to be the most prevalent causative agents of R-ICU infections. It is noteworthy that with an incidence as high as we have observed in our cohort, respiratory infection is still a very important source for respiratory infections of MDR pathogens in an ICUs setting.

One of the important conclusions of the present study was that the MDR infections had a tremendous higher mortality. We found similar results to those found by Bhat et al,[1] who showed that clinically Severe, non-severe, long-term stay, and death rates were significantly poorer for carbapenem-resistant Klebsiella pneumoniabacteremia cases compared to carbapenem-susceptible cases. Similarly, Howard-Anderson et al,[6] reported statistically poorer results for patients colonized or infected with carbapenem-resistant Enterobacterales (CRE), highlighting clinical consequences of resistance beyond microbiological failure. Furthermore, co-infections with CRE and other MDR bacteria, were reported to be associated with clinical deterioration and death by Tadese et al.[7] To summarize, our study is supported by these collective studies and we found that MDR infections – despite not being maple leaf blight infections – contribute by themselves to worse patient outcomes in critical care.

The higher rate of septic shock, acute kidney injury and mechanical ventilation occurrence in MDR-infected patients in the present wound study might be attributed to the delayed initiation of effective antimicrobial treatments and lack of availability for effective antimicrobial treatments. Resistant pathogens might lead to disease continuation until proper treatment can be treated and Sharma et al,[4] showed that colonization in the noses of these individuals with CRE increases the likelihood of subsequent invasive infection within the hospital setting, especially in the Intensive Care Unit, or nursery. Likewise, Suay-García and Pérez-Gracia,[14] noted the therapeutic difficulties associated with CRE infections and Fritzenwanker et al,[15] explained the limited options of therapeutic drugs effective against CREs. This may explain why the organ dysfunction of MDR-infected persons are increased, as well as the mortality rates.

Furthermore, patients with MDR infections had notably longer duration of ICU stay, hospital stay, mechanical ventilation and treatment expense. Patients affected by MDR infections had almost double the length of their hospital stay in the intensive care unit and cost significantly more for the care received than non-MDR patients.

This result is in line with the one found in Nelson et al,[8] where it is reported that people with MDR infections were more likely to die, to spend longer in hospital and to have a significantly higher cost of health care when they were hospitalised. In the same way, Wozniak et al,[9] found that antimicrobial-resistant infections are a significant economic cost to healthcare systems, in terms of the number of additional beds occupied, the cost of treating additional patients, and additional resource use. The higher number of diagnostic tests performed and the amount of antimicrobial use noted in our studies are further examples of the significant burden that MDR infections place on healthcare resources.

However, the burden of antimicrobial resistance (AMR) seen in the current study should also be considered in the global context. According to Murray et al,[12] the impact of antimicrobial resistance on mortality worldwide accounted for almost 4.95 million deaths in 2019, one of the leading causes of infectious disease mortality world-wide.

Similarly, one of Cass writable et al,[13] found that in Europe, there was a very high prevalence of antibiotic resistance in infections, including considerable attributable mortality and disability adjusted life-years. The complexity of the estimation of the burden of antimicrobial resistance was also highlighted by Naylor et al,[11] and de Kraker and Lipsitch,[10] as common consequences of antimicrobial resistance was always excess mortality, longer hospital stay, and increased healthcare expenditure. The results of the current study

serves as another set of data for the critical care population in a resource-limited environment, where the magnitude of the antimicrobial resistance problem can be greater.

The independent relationship of MDR infection with ICU mortality we found in our multivariable analysis stresses the importance of developing better antimicrobial stewardship (IPAC) programmes. Puraswani et al,[5] showed the potential of diversity in AMR with a surveillance study that lasted for eight years and highlighted the need for continuous monitoring and interventions for further evolution of the AMR trend. Optimization of antimicrobial prescription, rigorous control of infections, the early identification of MDR pathogens and fast microbiological diagnostics might be key to lowering death rates and the use of healthcare resources for MDR infections.

Limitations

There are some limitations of this study. First, this was performed in a single tertiary care center and may not be generalizable to other healthcare settings. Secondly, molecular characterisation of the resistance mechanisms was not undertaken, which hindered detailed study of the genetic causes of antimicrobial resistance. Third, residual confounding owing to severity of disease and previous exposure to antimicrobials cannot be fully ruled out, despite multivariable adjustment. Last but not least, assessments of long term post discharge results and indicators of quality of life were not made. However, a prospective design with detailed outcome assessment and evaluation of clinical and economic outcomes enhances the validity of the study results.

CONCLUSION

Multidrug-resistant infections pose a significant problem in ICUs and are linked to a significantly higher mortality rate in the ICUs, more days in the hospital, more organ support, and much more intensive use of health care resources. MDR infections were identified as an independent risk factor for mortality within the ICU setting in the present study, highlighting their negative effect in the critically ill. The high proportion of resistant Gram negative pathogens, and the ensuing expense associated with them, shows how much antimicrobial resistance is causing an economic burden on the clinic. The results highlight the need for effective infection prevention measures, antimicrobial stewardship initiatives, early microbiological testing and prompt and effective antimicrobial treatment to achieve better outcomes and reduced burdens of MDR infections in critical care units.

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