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Original Research Article

Multidrug Resistance Patterns and Associated Risk Factors in Ventilator-Associated Pneumonia: A Comprehensive Analysis

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Abstract:

Ventilator-associated pneumonia (VAP) is a common and serious complication among intubated patients in intensive care units (ICUs), often caused by multidrug-resistant (MDR) pathogens. This study aimed to determine the incidence of VAP in the ICU of a government hospital in India and assess the associated risk factors and bacterial pathogens. A prospective observational study was conducted over two years, including adult and adolescent patients requiring intubation and mechanical ventilation.

Methodology: A prospective observational study was conducted over two years in the ICU of a government hospital in India. Adult and adolescent patients (>14 years old) requiring intubation and mechanical ventilation were included. VAP was diagnosed using the clinical pulmonary infection score, considering clinical, laboratory, microbiological, and radiographic evidence.

Results: Out of 155 patients, 46 developed VAP (29.7%), with a calculated VAP rate of 22.14 events per 1000 ventilator days. Most VAP cases were late-onset, with a mean ICU stay before VAP development of 9.96 days. Gram-negative bacteria were the predominant pathogens, with MDR Acinetobacter being most commonly identified.

Conclusion: This study highlights the significant impact of multidrug-resistant (MDR) pathogens in ventilator-associated pneumonia (VAP) management in our ICU. The high prevalence of MDR organisms, particularly Gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter species, underscores the urgent need for effective infection control and antibiotic stewardship programs. Our findings indicate a notable presence of beta-lactamase-producing organisms, including ESBLs, AmpC beta-lactamases, and MBLs. Specifically, 21.43% of the isolates were ESBL producers, 28.57% were AmpC producers, and 25% were MBL producers. Key risk factors for MDR VAP identified include prolonged hospitalization (≥5 days), prior antibiotic therapy, and impaired consciousness. These results emphasize the necessity for continuous surveillance, early detection of resistance, and comprehensive infection control strategies to improve patient outcomes in the ICU setting.

Keywords: Ventilator-Associated Pneumonia, Intensive Care Unit, Multidrug-Resistant Pathogens, Acinetobacter, Infection Control, Antibiotic Stewardship.

Introduction

Ventilator-associated pneumonia (VAP) is a significant complication in patients admitted to Intensive Care Units (ICUs), contributing substantially to morbidity and mortality rates. Patients in ICUs are already critically ill, and the risk of secondary infections, particularly nosocomial infections, exacerbates their vulnerability. VAP, which occurs in patients who have been on mechanical ventilation for more than 48 hours, accounts for 86% of nosocomial pneumonia and can develop even after extubation. [1,2]

Classified as either early onset or late onset, VAP is primarily caused by a broad spectrum of bacterial pathogens. Common culprits include aerobic Gram-negative bacilli such as Pseudomonas aeruginosa, Acinetobacter species, Klebsiella pneumoniae, and Escherichia coli. Infections caused by Gram-positive cocci, particularly Staphylococcus aureus, are notably prevalent in patients with underlying conditions like diabetes mellitus and head trauma. [3,4] The prevalence and types of multidrug-resistant (MDR) pathogens implicated in VAP vary based on factors such as hospital admission rates, patient demographics, antibiotic exposure, and ICU characteristics, underscoring the importance of continuous local surveillance. [5]

Timely and accurate diagnosis of VAP, followed by the administration of appropriate antibiotic ther-

apy, is critical. Studies have consistently shown that delays in administering the correct antibiotic treatment significantly increase mortality rates. [6,7] Conversely, the initial prescription of an ineffective antibiotic regimen also elevates the risk of death. Given these high stakes, the need for timely surveillance data on the prevalence and resistance patterns of VAP pathogens is imperative.

This study was conducted to address the gap in localized data on the bacterial etiology of VAP in our institute. A hospital-based, prospective, observational study was carried out in the Department of Microbiology in the ICU of the Department of Critical Care Medicine at GMC and Hospital, Nagpur, India, over a period of two years (January 2022 to December 2023). The objectives were to determine the prevalence and risk factors of MDR pathogens among VAP patients, to assess their antibiotic susceptibility patterns, and to detect the presence of extended-spectrum β-lactamases (ESBL), AmpC β-lactamases, carbapenemases, and metallobetalactamases in these pathogens. This study aims to provide crucial insights that can guide effective clinical management and intervention strategies for VAP in our healthcare setting.

Methodology

This hospital-based, prospective, observational study was conducted in the Department of Microbiology within the ICU of the Department of Critical Care Medicine at GMC and Hospital, Nagpur, India, spanning two years from January 2022 to December 2023. The study included patients aged 18 years and above who were admitted to the ICU, mechanically ventilated for more than 48 hours, and subsequently developed pneumonia. Patients with pneumonia at the time of ICU admission or with other significant concurrent infections were excluded.

Data were collected using standardized forms, capturing patient demographics, underlying medical conditions, clinical presentation, and laboratory results, including age, gender, comorbid conditions, duration of mechanical ventilation, clinical signs and symptoms of pneumonia, and microbiological data from blood cultures, endotracheal aspirates, and sputum samples.

Respiratory specimens were aseptically collected from suspected VAP patients and processed in the microbiology laboratory using standard protocols. The specimens were cultured on appropriate media, incubated under suitable conditions, and bacterial pathogens were identified using conventional biochemical tests and automated systems like VITEK 2. Antibiotic susceptibility was determined using the Kirby-Bauer disk diffusion method and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The presence of extended-spectrum β-lactamases (ESBL), AmpC β-lactamases, carbapenemases, and metallobetalactamases was detected using methods such as the double-disk synergy test (DDST), disk approximation test, modified Hodge test (MHT), Carba NP test, combined disk test (CDT), and E-test.

Statistical analysis was performed using SPSS software version 25.0. Descriptive statistics summarized patient demographics, clinical characteristics, and microbiological data. The prevalence of MDR pathogens was calculated, and risk factors for MDR VAP were identified using multivariate logistic regression analysis. Antibiotic susceptibility patterns were analyzed to determine resistance rates among the isolates. The study adhered to ethical standards, receiving approval from the Institutional Ethics Committee of GMC and Hospital, Nagpur, and obtaining informed consent from all participants or their legal guardians.

The study findings, detailed in the results section, provide valuable insights into the prevalence of MDR pathogens, their antibiotic susceptibility patterns, and the presence of ESBL, AmpC β-lactamases, carbapenemases, and metallobetalactamases, guiding effective clinical management and intervention strategies for VAP in the ICU setting.

Results

Table 1: Distribution of Organisms According to Onset of VAP in Culture-Confirmed VAP-Positive Patients (n=65)

Organism	Early-onset VAP (n=21) (%)	Late-onset VAP (n=38) (%)	Total (%)
Pseudomonas aeruginosa	7 (30.43)	11 (28.95)	18 (27.69)
Acinetobacter spp	4 (17.39)	10 (26.32)	14 (21.54)
Klebsiella pneumoniae	4 (17.39)	8 (21.05)	12 (18.46)
Escherichia coli	3 (13.04)	6 (15.79)	9 (13.85)
Enterobacter spp	1 (4.35)	1 (2.63)	2 (3.08)
Methicillin Sensitive Staphylococcus aureus (MSSA)	2 (8.70)	3 (7.89)	5 (7.69)
Methicillin Resistant Staphylococcus aureus (MRSA)	0 (0)	1 (2.63)	1 (1.54)
Enterococcus faecalis	2 (8.70)	1 (2.63)	3 (4.61)
Citrobacter freundii	0 (0)	1 (2.63)	1 (1.54)

Table 1 presents the distribution of organisms identified in culture-confirmed VAP-positive patients (n=65), categorized by early-onset and late-onset VAP. Among the 65 patients, 21 developed early-onset VAP and 38 developed late-onset VAP.

Pseudomonas aeruginosa was the most frequently isolated pathogen, accounting for 30.43% of early-onset VAP cases and 28.95% of late-onset VAP cases, with an overall prevalence of 27.69%. Acinetobacter species were the second most common, identified in 17.39% of early-onset cases and 26.32% of late-onset cases, resulting in an overall prevalence of 21.54%. Klebsiella pneumoniae was found in 17.39% of early-onset and 21.05% of late-onset VAP cases, comprising 18.46% of the total isolates. Escherichia coli accounted for 13.04% of early-onset and 15.79% of late-onset cases, with a total prevalence of 13.85%. Enterobacter species were less common, with 4.35% in early-onset and 2.63% in late-onset cases, totaling 3.08%. Methicillin Sensitive Staphylococcus aureus (MSSA) was identified in 8.70% of early-onset and 7.89% of late-onset VAP cases, representing 7.69% of the total. Methicillin Resistant Staphylococcus aureus (MRSA) was found only in late-onset VAP cases, at 2.63%, contributing to 1.54% overall.

Enterococcus faecalis was isolated in 8.70% of early-onset and 2.63% of late-onset cases, with an overall prevalence of 4.61%. Lastly, Citrobacter freundii was identified only in late-onset VAP cases, at 2.63%, accounting for 1.54% of the total isolates.

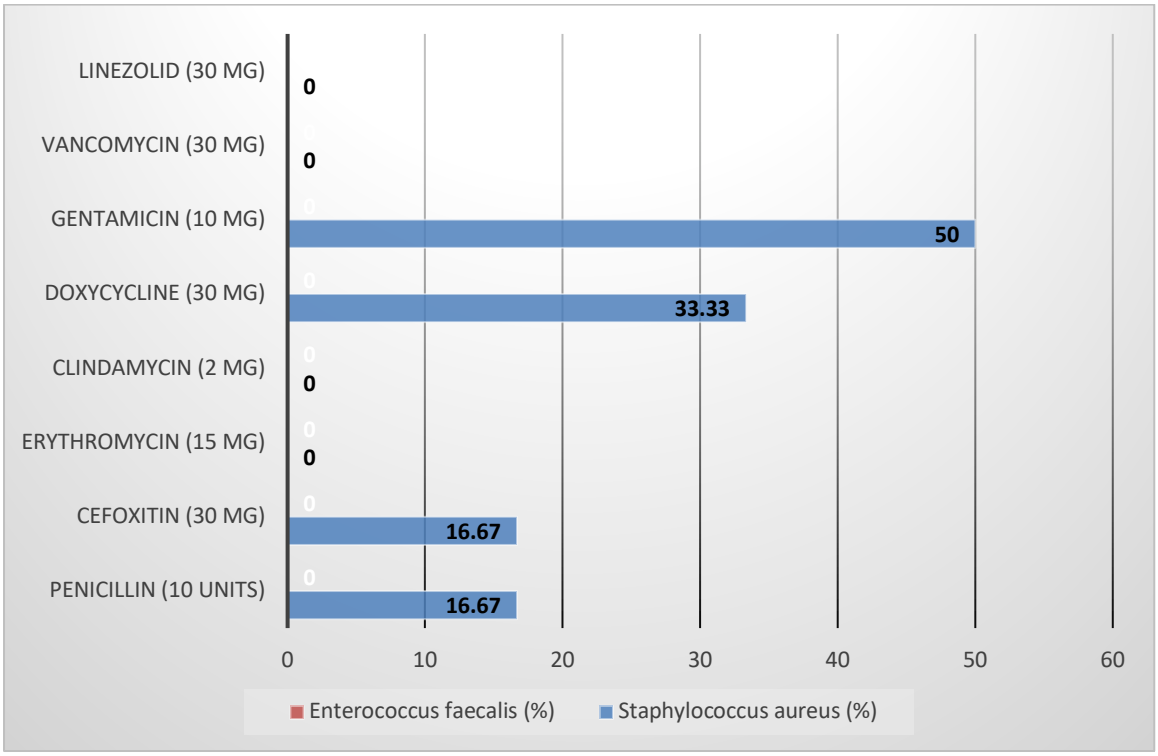

Figure 1: Antimicrobial Resistance Pattern of Gram-Positive Isolates in Culture-Confirmed VAP-Positive Patients (n=9)

Among the Staphylococcus aureus isolates (n=6), resistance was observed as follows: 16.67% to penicillin, 16.67% to cefoxitin, 33.33% to doxycycline, and 50% to gentamicin.

No resistance was noted to erythromycin, clindamycin, vancomycin, or linezolid. For Enterococcus faecalis isolates (n=3), no resistance was detected to any of the antibiotics tested, including penicillin, doxycycline, and gentamicin. Additionally, there was no resistance to erythromycin, clindamycin, vancomycin, or linezolid.

This data indicates a notable level of resistance among Staphylococcus aureus isolates to penicillin, cefoxitin, doxycycline, and gentamicin. However, the Enterococcus faecalis isolates exhibited susceptibility to all tested antibiotics.

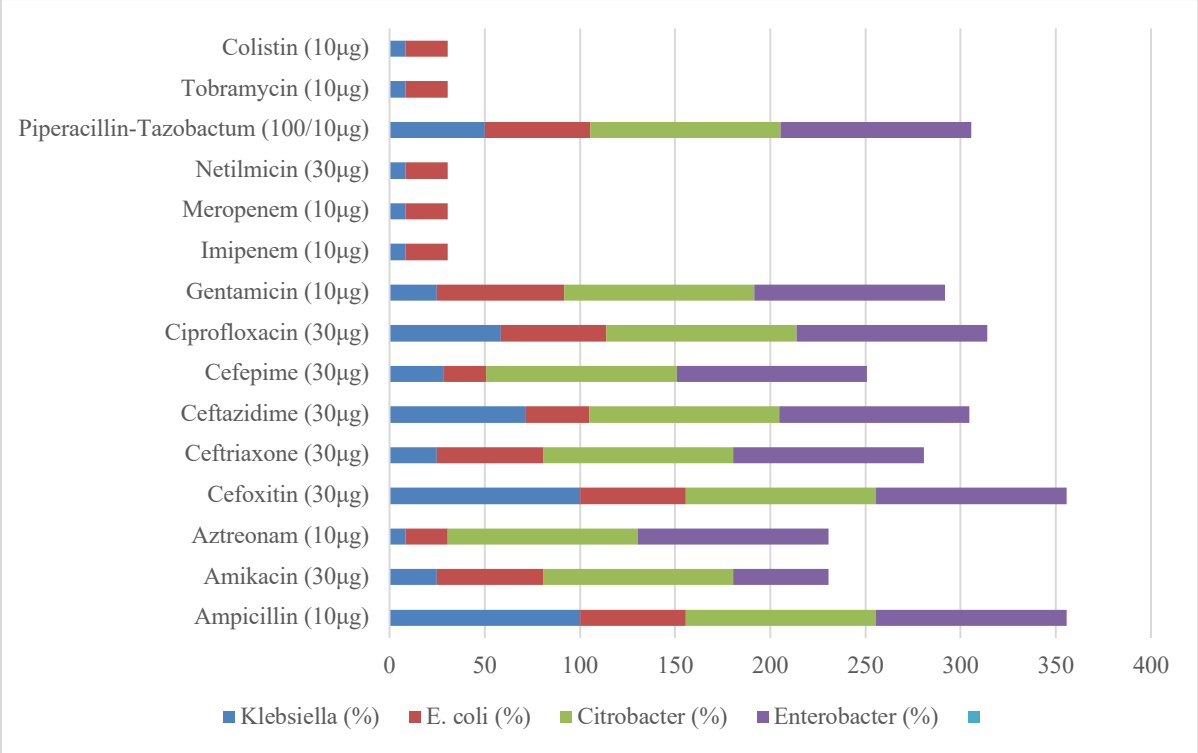

Figure 2: Antimicrobial Resistance Pattern among Enterobacteriaceae Isolates in VAP-Positive Patients (n=24)

Among the 24 Enterobacteriaceae isolates from VAP-positive patients, high resistance was observed to ampicillin (83.33%), cefoxitin (83.33%), and ciprofloxacin (62.50%). Moderate resistance was seen with gentamicin (50.00%), ceftriaxone (45.83%), and ceftazidime (45.83%). Lower resistance rates were noted for amikacin (41.67%), aztreonam (25.00%), and cefepime (29.17%). Imipenem, meropenem, netilmicin, and tobramycin showed the lowest resistance (12.50%). Colistin displayed a 12.50% resistance rate, but data for Citrobacter isolates were not available. These findings highlight the varying resistance patterns among Enterobacteriaceae isolates, emphasizing the need for prudent antibiotic use to combat VAP.

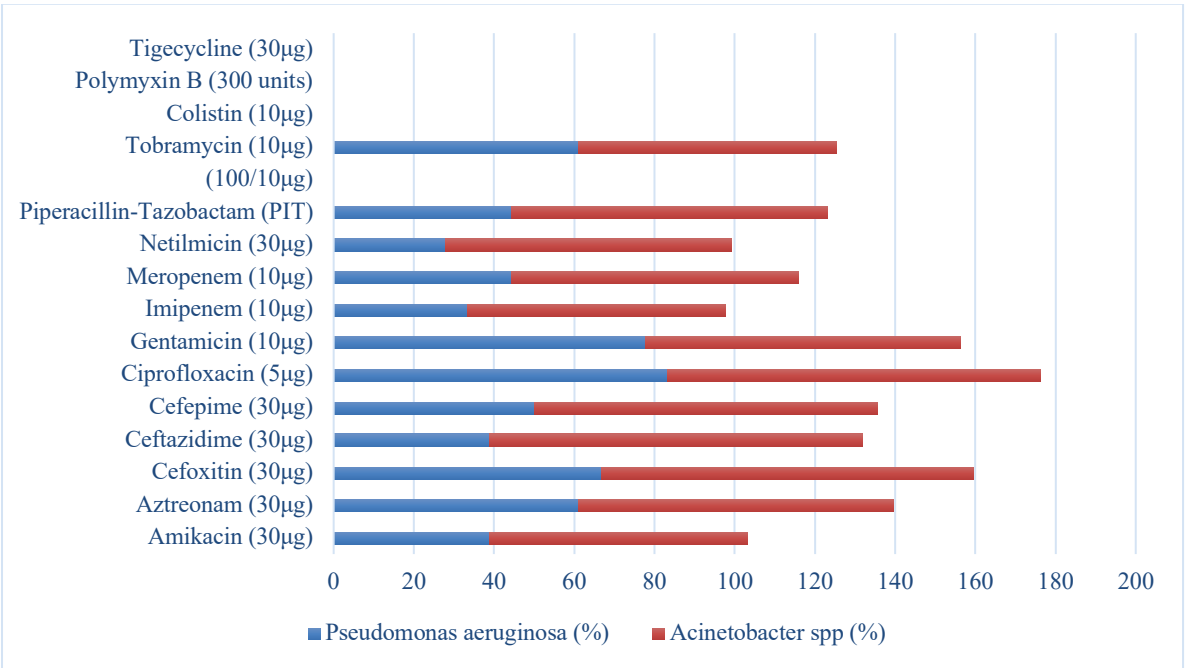

Figure 3: Antimicrobial Resistance Pattern in Non-Fermenter Isolates in VAP-Positive Patients (n=32)

The fig 3 presents the antimicrobial resistance pattern among non-fermenter isolates in VAP-positive patients (n=32). Pseudomonas aeruginosa showed varying degrees of resistance, with higher rates observed for ciprofloxacin (83.33%), cefoxitin (66.67%), and ceftazidime (38.89%). Acinetobacter spp exhibited high resistance rates to cefoxitin (92.9%), ciprofloxacin (92.9%), and ceftazidime (92.9%). Overall, both pathogens displayed considerable resistance to most antibiotics tested, emphasizing the challenge in treating VAP caused by these organisms. Notably, colistin and polymyxin B showed no resistance, highlighting their importance as last-resort treatment options.

Table 2: Distribution According to Beta-Lactamase Production in Isolates in VAP-Positive Patients

Beta-lactamase Type	Pseudomonas aeruginosa (%)	Acinetobacter species (%)	Klebsiella pneumoniae (%)	Escherichia coli (%)	Enterobacter species (%)	Citrobacter freundii (%)	Total (%)
ESBL	-	-	7 (58.33)	3 (33.33)	1 (50.00)	1 (100)	12 (21.43)
AmpC	6 (33.33)	10 (71.42)	0 (00)	0 (00)	0 (00)	0 (00)	16 (28.57)
ESBL + AmpC	0 (00)	0 (00)	5 (41.67)	3 (33.33)	1 (50.00)	0 (00)	6 (10.71)
MBL	6 (33.33)	7 (50.00)	2 (25.00)	0 (00)	0 (00)	0 (00)	14 (25.00)

The table illustrates the distribution of beta-lactamase production among bacterial isolates from VAP-positive patients. Among Pseudomonas aeruginosa isolates, 33.33% were positive for AmpC beta-lactamase and metallo-beta-lactamase (MBL) each. Acinetobacter species showed a higher prevalence of AmpC beta-lactamase production at 71.42% and MBL at 50.00%. Klebsiella pneumoniae exhibited a significant presence of extended-spectrum beta-lactamase (ESBL) at 58.33% and a lower but notable presence of ESBL combined with AmpC beta-lactamase at 41.67%. In Escherichia coli, 33.33% were positive for ESBL, and 33.33% for ESBL combined with AmpC beta-lactamase. Enterobacter species had a high incidence of ESBL (50.00%) and AmpC beta-lactamase (50.00%). Citrobacter freundii showed 100% positivity for ESBL. Overall, these findings highlight the diverse beta-lactamase profiles among different bacterial species causing VAP, emphasizing the importance of tailored antibiotic therapy based on local resistance patterns.

Table 3: Risk Factors for MDR in VAP Patients

Risk Factor	MDR (%)	Non-MDR (%)	Relative Risk	P-value
Hospitalization of 5 or more days	59.18	12.5	1.59	0.001
Prior antibiotic therapy	67.34	25	1.56	0.003
Impaired consciousness	24.48	6.25	1.3	0.12
Neurological disorders	20.4	18.75	1.07	0.82
Surgery	8.16	6.25	1.12	0.68
Steroid therapy	22.44	0	1.43	0.07

The table presents the risk factors associated with multidrug-resistant (MDR) infections in ventilator-associated pneumonia (VAP) patients.

Among these factors, hospitalization for 5 or more days and prior antibiotic therapy stand out as significant contributors to MDR, with 59.18% and 67.34% of MDR cases respectively, compared to much lower percentages in non-MDR cases (12.50% and 25.00% respectively). These factors show a relative risk of 1.59 and 1.56 respectively, with p-values indicating a high level of significance (p=0.001 and p=0.003 respectively). Impaired consciousness, neurological disorders, surgery, and steroid therapy also show differences between MDR and non-MDR cases, although with varying degrees of significance.

These findings underscore the importance of considering these risk factors in the management and treatment of VAP to minimize the emergence and spread of MDR pathogens.

Table 4: Adjusted Odds Ratios for Risk Factors in VAP Patients

Risk Factor	Adjusted Odds Ratio	Confidence Interval		P-value
		Lower	Upper	
Hospitalization of 5 or more days	10.15	1.86	72.93	0.004
Prior antibiotic therapy	6.91	1.51	37.44	0.02

The table presents the adjusted odds ratios (AOR) for two key risk factors in ventilator-associated pneumonia (VAP) patients. Hospitalization for 5 or more days shows a significantly increased likelihood of MDR infection, with an AOR of 10.15 (95% CI: 1.86 - 72.93) and a p-value of 0.004. Similarly, prior antibiotic therapy is associated with a higher risk of MDR, with an AOR of 6.91 (95% CI: 1.51 - 37.44) and a p-value of 0.02. These findings suggest that prolonged hospitalization and previous antibiotic exposure are strong predictors of multidrug-resistant infections in VAP patients, highlighting the importance of judicious antibiotic use and infection control measures in this population.

Discussion

The present study highlights the significant prevalence of ventilator-associated pneumonia (VAP) in our ICU and underscores the dominance of multidrug-resistant (MDR) pathogens among these infections. This finding is consistent with global trends, where MDR organisms pose a significant challenge in managing VAP due to their resistance to multiple antibiotic classes.

Our results demonstrate that Gram-negative bacilli, particularly Pseudomonas aeruginosa and Acinetobacter species, are the predominant pathogens in VAP cases. These pathogens are known for their inherent resistance mechanisms and their ability to acquire additional resistance genes. The phenotypic detection of resistance mechanisms, such as extended-spectrum beta-lactamases (ESBLs), AmpC beta-lactamases, and metallo-beta-lactamases (MBLs), was a critical aspect of our study. We found that 21.43% of the isolates were ESBL producers, 28.57% were AmpC producers, and 25% were MBL producers. This high prevalence of beta-lactamase-producing organisms significantly complicates treatment options and outcomes.

This is consistent with previous studies highlighting the importance of these pathogens in VAP. The study by Hassan et al. [8] conducted in Bahrain highlights several key findings that resonate with our study on ventilator-associated pneumonia (VAP). Firstly, they reported a relatively high VAP rate of 22.14 events per 1000 ventilator days, which underscores the importance of VAP prevention strategies. Similarly, our study identified a high prevalence of multidrug-resistant (MDR) pathogens in VAP patients, emphasizing the urgent need for appropriate antibiotic use and stewardship programs. Furthermore, both studies highlight the predominance of Gram-negative bacteria as the causative agents of VAP. In particular, both studies noted the significance of multidrug-resistant Acinetobacter as a major pathogen, suggesting a common trend in the microbial etiology of VAP in different settings. Overall, the findings of Hassan et al. and our study support the importance of ongoing surveillance and prevention efforts to reduce the burden of VAP and improve patient outcomes.

The presence of ESBL-producing organisms, particularly among Klebsiella pneumoniae and Escherichia coli, is concerning as it limits the efficacy of beta-lactam antibiotics, which are often first-line treatments for Gram-negative infections. Similarly, the detection of AmpC beta-lactamase producers indicates resistance to a broader range of beta-lactam antibiotics, including cephamycins and beta-lactamase inhibitor combinations, necessitating the use of carbapenems or other non-beta-lactam antibiotics. However, the emergence of MBLs among our isolates further restricts the use of carbapenems, often considered the last resort for treating severe Gram-negative infections.

The risk factors associated with MDR VAP in our study included prolonged hospitalization (more than five days), prior antibiotic therapy, and impaired consciousness. These factors have been consistently identified in other studies as significant contributors to the development of MDR infections. Prolonged hospital stays increase the exposure to nosocomial pathogens and antibiotic pressure, facilitating the selection of resistant strains. Prior antibiotic therapy, particularly with broad-spectrum agents, disrupts normal flora and selects for resistant organisms. Impaired consciousness, often leading to prolonged mechanical ventilation and the need for invasive procedures, further elevates the risk of VAP and subsequent MDR infections.

Our findings align with those of Vaithiyam et al. [9], who reported a high prevalence of MDR organisms in clinical isolates from a tertiary care hospital in India, emphasizing the need for stringent antibiotic stewardship and infection control measures to mitigate the spread of these resistant pathogens . Similarly, Wu et al. highlighted the significant impact of prolonged mechanical ventilation and prior antibiotic use on the incidence of VAP, underscoring the importance of targeted interventions to reduce these risk factors.

Risk factor analysis revealed that prolonged hospitalization (≥5 days) and prior antibiotic therapy were significantly associated with MDR infections in VAP patients. These findings are consistent with previous studies demonstrating the role of these factors in the development of MDR infections. he review by Wu et al. [10] provides valuable insights into the risk factors for ventilator-associated pneumonia (VAP) and the strategies used to prevent this condition. Several risk factors discussed in the review, such as prolonged

mechanical ventilation time, prior antibiotic therapy, and invasive operations, are consistent with the findings of our study. The review also highlights the importance of patient characteristics, comorbidities, and gene polymorphisms as risk factors for VAP, which are factors that were not explicitly addressed in our study but are nonetheless relevant in understanding the complexity of VAP risk assessment. Furthermore, the review emphasizes the role of preventive measures, such as the use of chlorhexidine, β-lactam antibiotics, and probiotics, in reducing the incidence and mortality rate of VAP. While our study did not specifically investigate the effectiveness of these preventive strategies, the review's findings support the importance of implementing comprehensive preventative strategies to reduce the burden of VAP. In conclusion, the review by Wu et al. provides a comprehensive overview of the risk factors for VAP and the strategies used to prevent this condition. The findings of our study, particularly regarding the impact of prolonged hospitalization and prior antibiotic therapy on MDR infections in VAP, are consistent with the broader literature on VAP risk factors. These findings highlight the importance of ongoing research and clinical efforts to improve the prevention, diagnosis, and management of VAP. The association between prior antibiotic therapy and MDR infections highlights the importance of antibiotic stewardship practices in reducing the emergence and spread of MDR pathogens in healthcare settings (Reference 4).

Antimicrobial resistance testing showed high rates of resistance among Gram-negative isolates, particularly against commonly used antibiotics such as ciprofloxacin, ceftazidime, and imipenem. This emphasizes the need for local surveillance data to guide empiric antibiotic therapy in VAP patients, as the choice of initial antibiotic therapy can significantly impact patient outcomes. The study by Vaithiyam et al. [9] highlights the high prevalence of multidrug-resistant organisms (MDROs) in medical wards of a tertiary care hospital in India.

Their findings of 27% of isolates showing multidrug resistance (MDR) and 61% showing possible extremely drug-resistance pattern are consistent with the challenges identified in our study regarding the prevalence of MDR pathogens in ventilator-associated pneumonia (VAP) patients. Both studies underscore the urgent need for appropriate antibiotic usage and the implementation of antibiotic stewardship programs to combat the rising threat of MDROs. The high prevalence of MDR pathogens in both hospital settings emphasizes the importance of understanding local resistance patterns and tailoring treatment strategies accordingly to improve patient outcomes and reduce the burden of antibiotic resistance.

Conclusion

This study underscores the significant challenge posed by multidrug-resistant (MDR) pathogens in the management of ventilator-associated pneumonia (VAP) within our ICU. The high prevalence of MDR organisms, particularly Gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter species, highlights the critical need for robust infection control measures and effective antibiotic stewardship programs. Our findings reveal a notable presence of beta-lactamase-producing organisms, including extended-spectrum beta-lactamases (ESBLs), AmpC beta-lactamases, and metallo-beta-lactamases (MBLs). Specifically, 21.43% of the isolates were ESBL producers, 28.57% were AmpC producers, and 25% were MBL producers. These resistance mechanisms significantly limit the therapeutic options available, necessitating more precise and targeted antimicrobial therapies.

The study identifies key risk factors associated with the development of MDR VAP, including prolonged hospitalization (≥5 days), prior antibiotic therapy, and impaired consciousness. These factors have been consistently associated with an increased risk of acquiring MDR infections, emphasizing the importance of early identification and management to improve patient outcomes.

In conclusion, the high incidence of MDR pathogens and the prevalence of complex resistance mechanisms in VAP patients underscore the need for continuous surveillance, early phenotypic detection of resistance, and the implementation of comprehensive infection control strategies. Addressing these challenges through stringent antibiotic stewardship and tailored therapeutic interventions is crucial in mitigating the impact of MDR organisms on patient morbidity and mortality in the ICU setting.

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