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ORIGINAL RESEARCH ARTICLE

"Identification and Antibiotic Susceptibility Patterns of Non-Fermentative Gram-Negative Bacilli in Ventilator-Associated Pneumonia: A Hospital ICU Study Emphasizing Multidrug Resistance"

[1]Neha Goel, [2]Shadab Samad, [3]Sagar Kashyap, *[4]Dimpal Rochlani

[1]Associate Professor, Department of Microbiology, GS Medical College & Hospital, Pilkhuwa, Hapur, U.P. India

[2]Assistant Professor, Department of General Medicine, GS Medical College & Hospital, Pilkhuwa, Hapur, U.P. India

[3]Assistant Professor, Department of Microbiology, GS Medical College & Hospital, Pilkhuwa, Hapur, U.P. India

*[*4]Assistant Professor, Department of Biochemistry, GS Medical College & Hospital, Pilkhuwa, Hapur, U.P. India*

Author for Correspondence

Dr. Dimpal Rochlani

dimpal.rochlani8@gmail.com

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ABSTRACT:

Background: Ventilator-associated pneumonia (VAP) caused by non-fermenting Gram-negative bacilli (NFGNB) poses a significant threat in intensive care units (ICUs), contributing to elevated mortality and morbidity rates. This study aims to characterize the multidrug resistance (MDR) patterns of NFGNB implicated in VAP.

Methods: A cross-sectional analysis was conducted among VAP patients admitted GSMCH, Pilkhuwa. Antibiotic susceptibility profiles were determined using the minimum inhibitory concentration (MIC) test via the broth microdilution method.

Results: Patients were categorized into infected and non-infected groups based on culture results, revealing that 37 patients (18.5%) were infected. Among the 37 microbiologically confirmed VAP cases, 17 NFGNBs (11 P. aeruginosa and 06 A. baumannii) were identified as causative agents. Specifically, MDR NFGNBs included 05 A. baumannii and 09 P. aeruginosa isolates. Resistance rates among P. aeruginosa were notable, with resistance observed against all aminoglycosides, ciprofloxacin, ceftazidime, cefepime, colistin, and imipenem. Similarly, A.

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baumannii exhibited high resistance rates, particularly against aminoglycosides, ciprofloxacin, ceftazidime, cefepime, colistin, and imipenem.

Conclusion: The alarming prevalence of multidrug resistance underscores the urgent need for effective therapeutic strategies. Implementation of antibiotic stewardship programs in healthcare settings is crucial to mitigate the dissemination of MDR bacteria.

Keywords: Multidrug resistance; Antibiotic; Ventilator-associated pneumonia; Endotracheal tube; Nosocomial infection.

Introduction:

Ventilator-associated pneumonia (VAP) remains a critical concern in intensive care units (ICUs), posing significant mortality risks among mechanically ventilated patients (Papazian *et al.,* 2020). Despite advancements in treatment modalities, VAP persists as a prominent nosocomial infection, comprising a quarter of all ICU infections globally (Divatia *et al.,* 2019). Its toll includes prolonged hospital stays, escalated antibiotic usage, heightened treatment expenses, and an estimated 13% mortality rate. Notably, male patients' exhibit a 1.3 times higher susceptibility to VAP, attributed to multifaceted factors such as sex hormone variations and genetic predispositions (Wu *et al.,* 2019). VAP is stratified into early and late onset categories, necessitating prompt and tailored antibiotic interventions to mitigate mortality risks. However, indiscriminate antibiotic use fosters resistance, compounding treatment challenges and costs (Nora and Povoa, 2017).

The intricate interplay between endotracheal tube presence, biofilm formation, and microbial colonization underscores the complexity of VAP pathogenesis. Microbiological surveillance, coupled with oral decontamination strategies, holds promise in reducing VAP incidence. Furthermore, specific patient cohorts, including hemodialysis recipients and those with recent antibiotic exposure, are at heightened risk of acquiring drug-resistant pathogens.

Treating ventilator-associated pneumonia (VAP) caused by multidrug-resistant (MDR) species poses significant challenges due to the co-resistance of these pathogens to commonly used antibiotics (Vo *et al.,* 2022). This situation has resulted in a scarcity of effective treatment options. The diminishing effectiveness of routinely-prescribed antibiotics on a global scale can be largely attributed to the prevalence of extended-spectrum beta-lactamases and carbapenem hydrolyzing enzymes (Husna *et al.,* 2023). The rise in MDR non-fermenting Gram-negative bacteria (NFGNB) isolates may be linked to the acquisition or horizontal transfer of antibiotic resistance genes. Integrons, acting as movable genetic entities, possess the capability to acquire and disseminate genes conferring resistance to antimicrobials. Among the five identified classes of integrons, class 1 predominates in clinical isolates, rendering the strains harboring these genes resistant to various antimicrobial classes (Lorestani *et al.,* 2018). Numerous studies have documented elevated occurrences of ventilator-associated pneumonia (VAP) attributed to multidrug-resistant non-fermenting Gram-negative bacteria (MDR NFGNB). Conversely, understanding the local epidemiology of these pathogens is crucial.

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Variability in microbial etiology across patient populations and healthcare settings underscores the need for context-specific research. In this context, our study addresses a critical gap in the literature by comprehensively evaluating non-fermentative gram-negative bacilli in VAP within our ICU setting. By elucidating their antibiotic susceptibility profiles, with a focus on multidrug resistance, we aim to inform targeted therapeutic strategies and enhance patient outcomes in our hospital setting.

Material and methods:

Study Setting and Methodology: At the Department of Microbiology, located in (M.P), India, a prospective hospital-based cross-sectional study was undertaken. The study cohort comprised 200 patients diagnosed with ventilator-associated pneumonia. Over a span of 72 hours, these individuals received mechanical ventilation. Lower respiratory tract samples, obtained via endotracheal aspiration (ETA) and bronchoalveolar lavage (BAL), along with chest radiographs, were collected. Both ETA and BAL samples were promptly transported to the laboratory for semi-quantitative bacterial culture and direct gram staining. Ethical clearance for this study was obtained from the institutional ethics committee, and written informed consent was obtained from the patients' caregivers.

Study Population: Eligibility criteria encompassed a minimum of 48 hours of mechanical ventilation, along with radiological evidence (temperature exceeding 38˚C or 100.4˚ F), leukopenia, and pulmonary indicators such as worsening gas exchange, cough, dyspnea, or tachypnea, accompanied by rails or bronchial breath sounds. Additionally, the presence of new-onset purulent sputum, changes in sputum character, increased respiratory secretions, or heightened suctioning requirements were required.

Deep tracheal aspirates were collected from endotracheal tubes by head nurses and promptly transported to the microbiology laboratory in sterile containers. Subsequently, samples were cultured on blood agar, chocolate agar, and MacConkey's agar, followed by incubation at 37˚C for 24 hours. Identification of NFGNB was conducted using standard microbiological protocols.

Data collection: A comprehensive patient history was meticulously collected using a structured questionnaire. These included pertinent details such as patient's name, age, gender, underlying medical condition, date of admission, history of previous hospitalizations, duration of ventilation, length of hospital stay, and demographic data. Additionally, the clinical outcome of each patient was meticulously documented. In cases of recurrent suspected ventilator-associated pneumonia (VAP), only the initial episode was considered for analysis.

Collection of Endotracheal aspirates (ETA) (Raut *et al.*, 2015)

Employing aseptic measures, we gathered endotracheal aspirates utilizing a 22-inch suction catheter of No.12F dimensions, channeling them into a mucus collector. With precision, the catheter was inserted through the endotracheal tube, reaching a depth of roughly 25-26cm. Following this, we gently applied suction without saline introduction, withdrawing the catheter from the endotracheal tube thereafter. Subsequently, 2mL of normal saline was carefully injected via a sterile syringe to flush the exudate into a sterile container designated for collection.

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Collection of Bronchioalveolar lavage (BAL) (Davidson *et al.,* 2020)

In this process, a substantial quantity of saline (ranging from 100 to 300ml) was introduced into a specific lung segment via a bronchoscope by the bronchoscopist. This was done to collect cells and proteins from the pulmonary interstitium and alveolar spaces. Following infusion, the saline is aspirated into a sterile container and forwarded for microbiological analysis.

Respiratory samples (including ETA and BAL) underwent mechanical homogenization via vortexing for one minute before undergoing the subsequent microscopic examination using conventional laboratory techniques.

Microbiological analysis:

Microbiological analysis was conducted on ETA Gram stains, viewed under high power field at a magnification of 1000x, with results indicating the presence of specific bacteria, yeasts, and/or oropharyngeal flora. Semiquantitative culture of ETAs was performed; BAL Gram stain results were expressed as the count of bacteria per high power field. BAL samples were excluded if they met any of the predefined rejection criteria. Included BAL samples underwent analysis according to a meticulously standardized protocol, involving the identification of intracellular organisms (ICOs) per 500 nucleated cells on May-Grünwald-Giemsa-stained cytospin preparations, expressed as a percentage, and quantitative cultures reported as CFU/ml.

The samples underwent culturing on blood agar, chocolate agar, and MacConkey's agar, followed by an incubation period at 37°C for 24 hours. Subsequent identification of Non-Fermenting Gram-Negative Bacilli (NFGNB) was carried out in accordance with established microbiological protocols.

Antibiotic Susceptibility Testing, MDR-NFGNB Isolation, and Co-Resistance Profiling (Bagheri-Nesami *et al.,* 2017)

The process involved conducting antibiotic susceptibility tests, isolating Multi-Drug Resistant (MDR) Non-fermenting Gram-Negative Bacilli (NFGNB), and determining their co-resistance profiles. Antibiotic susceptibility testing was carried out using the standard broth microdilution techniques following the CLSI 2010 protocol. Bacterial suspension equivalent to 0.5McFarland standard were prepared in Muller-Hinton broth, with final bacterial concentrations adjusted to $5x10^5$ CFU/ml. Serial concentrations of antibiotics ranging from 512µg/mL to 1µg/mL were prepared. The tested antibiotics included amikacin (AN), ciprofloxacin (CP), imipenem (IPM), gentamicin (GM), ceftazidime (CAZ), tobramycin (TOB), piperacillin-tazobactam (TZP), cefepime (CPM), colistin (CST), and co-trimoxazole (TMP/SMX).

Statistical analysis: Statistical Package for Social Science (SPSS, Chicago, IL, USA) version 20.0 and Excel (Microsoft 13) were used for the data analysis. The results were expressed as Mean ± Standard Deviation. The p-value < 0.05 was considered statistically significant.

Results:

Study Enrollment: Throughout the study duration, we included 200 consecutive patients aged between 18 and 60 years, comprising 147 men and 53 women. The primary indications for requiring ventilator support varied, including multisystem trauma (n=38), postoperative respiratory failure (n=31), exacerbation of chronic obstructive pulmonary disease (n=24), severe

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sepsis (n=27), multiple organ failure (n=12), neurological emergencies (n=13), other pulmonary diseases (n=35), and acute pancreatitis (n=20). Bacterial pneumonia was diagnosed in 37 cases. All bronchoscopies were conducted without complications, with no instances of hypoxemia, pneumothorax, or hemorrhage observed. Additionally, no significant hemodynamic changes were noted during or after the procedure in any patient.

Patients were categorized into infected and non-infected groups based on culture results, revealing that 37 patients (18.5%) were infected.

Table 1: Demographics of study population

	Study Population (200) [n (%)]	**Infected (37) [n (%)]**	**Non-infected (163) [n (%)]**
Age	47	52	49.5
31-40 (Male)	14	1	13
31-40 (Female)	1	0	1
41-50 (Male)	61	18	43
41-50 (Female)	29	6	23
51-60 (Male)	59	08	51
51-60 (Female)	21	3	18
>60 (Male)	13	1	12
>60 (Female)	2	0	02
Sex			
Male	147 (73.5)	28 (75.6)	119 (73.0)
Female	53 (26.5)	09 (24.3)	44(26.9)

The table illustrates that the average age of the study participants was 47 years, with the infected group averaging 52 years and the non-infected group averaging 49.5 years. In terms of gender distribution, males were predominant, constituting 75.6% of the infected patients**.**

Table 2: Growth in quantitative culture

Respiratory Samples	**Quantitative culture**	
	Threshold of pathogens	
	ETA≥10^5Cfu/ml	**BAL ≥10^5Cfu/ml**
Endotracheal aspirates (ETA)	33	NA
Bronchioalveolar lavage (BAL)	NA	4

Table 2 presents the findings of endotracheal aspirate (ETA) and bronchoalveolar lavage (BAL) cultures. Among all ETA samples, 33 exhibited pathogenic growth, whereas out of the total BAL samples, only 4 displayed pathogenic growth.

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Table 3: Distribution of organisms responsible among the subjects that developed VAP

Isolated Microorganism	No. of Patients	Percentage (%)
Escherichia coli	02	5.4
Acinetobacter spp.	06	16.2
Enterobacter spp.	01	2.7
Staphylococcus aureus	02	5.4
Klebsiella spp.	07	18.9
Pseudomonas spp.	11	29.7
Multibacterial Isolation		
Pseudomonas aeruginosa+ Staphylococcus aureus	02	5.4
Pseudomonas aeruginosa+ Klebsiella pneumonia	06	16.2

Table 3 displays the distribution of Gram-negative bacteria. Among all isolated organisms, Gram-negative bacteria were predominant in 35 cases, accounting for 94.5% of the total, as indicated in Table 3. Of the 18 subjects who developed ventilator-associated pneumonia (VAP) within 48 to 72 hours of initial ventilation, 19 subjects developed VAP after 72 hours. Notably, all cases of polymicrobial VAP (n=8) were instances of delayed-onset VAP.

Table 4: The number and percentage of Non fermentative Gram-negative bacteria

Non fermentative Gram-negative bacteria	Percentage (%)
Acinetobacter spp.	16.2
Pseudomonas spp.	29.7

Table 4 presents the count and proportion of non-fermentative Gram-negative bacteria. Among the 37 patients microbiologically diagnosed with ventilator-associated pneumonia (VAP), 17 cases were attributed to non-fermentative Gram-negative bacteria. Specifically, 6 cases were caused by *Acinetobacter spp.* and 11 cases by *Pseudomonas spp*.

Table 5: Multidrug Resistance Profiles of Non-Fermentative Gram-Negative Bacteria

Bacteria	No. of Isolates	Profile of NFGNB, resistance to different antibiotics
Acinetobacter spp. **(N=05)**	2 1 1 1	CPM, CAZ, IPM, MEP IPM, MEP, CAZ, CST CPM, CST, MEP, AN CST, IPM, MEP, IPM

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***Pseudomonas aeruginosa* (09)**	1 1 1 2 1 1 1	IPM, MEP, CAZ, TZP,CST MEP, CAZ, TZP,CST, IPM, CPM, CAZ, TZP, MEP, AMP, TZP, CAZ, MEP, MEP, CAZ, TZP, IPM,CST IPM, MEP, CAZ, TZP, CST CAZ, TZP, IPM, MEP, GM

AN-Amikacin; CAZ-Ceftrazidime; CP-Ciprofloxacin; CPM-Cefepime; CST-Colistin; IPM-Imipenem; GM-Gentamicin; TZP-piperacillin-tazobactam

Table 5 illustrates the multidrug resistance patterns of non-fermentative Gram-negative bacteria (NFGNB). Among these, the most commonly encountered multidrug-resistant NFGNBs were Acinetobacter spp. (n=05) and Pseudomonas aeruginosa (n=09).

Discussion

After more than 48 hours of mechanical breathing, a nosocomial infection known as ventilator-associated pneumonia (VAP) develops. VAP is a global issue causing changes in sputum features, systemic infection, new or progressive infiltrates, and the discovery of a causal agent. It is linked to death, longer hospital stays, costs, and financial burdens in underdeveloped countries (Papazian *et al.,* 2020, Kalanuria *et al.,* 2016). Variations in VAP rates are influenced by diagnostic criteria, ICU types, patient characteristics, causative bacteria, length of stay, and antibiotic use in hospitals (Papazian*et al.,* 2020). Kalanuria et al. (2016) predict a daily VAP incidence of 3% during the first five days of ventilation, 2% between days five and ten, and 1% after that, with a 45% decrease achievable through pneumonia prevention guidelines. In our investigation, there were 37 confirmed cases of VAP. Indian studies show varying incidence rates of VAP, with rates ranging from 13-42% (Joseph *et al.,* 2009). Vijay et al. (2018), reported 25-35% in underdeveloped nations and 15-17% in industrialized countries. The majority of patients are male and aged 40-50. Multisystem trauma and pulmonary disease patients have the highest percentage of cases, with 38% and 35% respectively. In the current study, late-onset VAP predominates over early-onset VAP. In Pondicherry, India, 72.2% of patients had early-onset VAP (Joseph *et al.,* 2013), while other studies in India show early-onset VAP in 20-40% and late-onset VAP in 3-60% (Mathai *et al.,* 2015). 72.8% of infections were caused by gram-negative bacteria, with 41% caused by Enterobacteriaceae, including 29.2% ESBL-producing strains in 63% of cases (Rawat and Nair, 2010). The current investigation identifies Gram-negative bacteria as the cause of VAP, consistent with previous studies (Medell*et al.,* 2013). These bacteria are becoming increasingly resistant to antibiotics, and the evolution of VAP due to NFGNB, particularly MDR strains, is concerning. Dellit's study found a prevalence of 42% NFGNB, which is linked to high mortality and morbidity. This raises concerns about the impact of NFGNB on VAP (Dellit, 2004). According to Gale et al. (2001) and Troillet et al. (1997), *P.*

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aeruginosa and *Acinetobacter species* are the most common nosocomial infections (Gales *et al.*, 2001; Troillet *et al.*, 1997). Similar observations have also been made by us. Non-fermenting Gram negative bacteria from the *Pseudomonas* and *Acinetobacter genera* made up 29.7% and 16.2% of the isolates, respectively. Global research on *A. baumannii* reveals high rates of colistin resistance in Asia-Pacific, Europe, North America, and Africa (Ahmed *et al.*, 2016).

According to a study by Wojkowska-Mach *et al.* (2009) comprising 2170 patients who underwent cardiac surgery and 2.2% of them were diagnosed with VAP, *Klebsiella pneumonia* (16.7%), *Escherichia coli* (12.6%), and *Pseudomonas aeruginosa* (10.4%) were the most frequently isolated bacteria. Gram negative bacteria were shown to be responsible for 71% of infections, whereas *Escherichia coli*, *Klebsiella pneumonia*, and ESBL-producing *Proteus mirabilis* were found to be 10% of infections in a study of 312 ICU patients, 40 of whom had been diagnosed with VAP. The lowest prevalence of *Klebsiella pneumonia* and ESBL-producing *Escherichia coli* strains was found in North America (12.7% and 4.7%, respectively), and ESBL producing strains have been reported from Latin America (45.5%) and Africa (54.9%), according to another study that examined 23,918 Gram negative bacterial strains sampled from ICU patients in six regions of the world. The susceptibility of *Pseudomonas aeruginosa* to the aforementioned antibiotic ranged from 79.1% in South America to 1.4% in Africa, while the susceptibility of *Acinetobacter baumannii* strains to meropenem ranged from 60.4% in North America to 1.9% in Africa (Bertrand and Dowzicky, 2012). According to previous Asian research (Joseph *et al.*, 2013), *P. aeruginosa* (24.1), *K. pneumonia* (24.1%), and *S. aureus* (7.5%) were the next most common bacteria in VAP cases after multidrug-resistant *A. baumannii.* The most prevalent agents in late-onset VAP were *A. baumannii* (32.2%), *P. aeruginosa* (29.4%), *K. pneumonia* (20.3%), and *E. coli* (5.6%), while the most frequent agents in early-onset VAP were *K. pneumonia* (36.4%) and *A. baumannii* (20.5%). However, the likely reason for this variation remained a mystery. The majority of patients in our study had monomicrobial infections, and only a small number of patients had polymicrobial infections, which often have bad prognosis. Since understanding the pattern of antibiotic resistance may help in treating VAP infection, it is vital to be aware of how susceptible microorganisms are to antimicrobial drugs. In the current investigation, *Pseudomonas spp* was the microbe that was most frequently isolated. (29.7%), followed by *Klebsiella pneumonia* (18.9%) and *Acinetobacter spp.* (16.2%). The proportion of various bacterial infections obtained from various types of samples varies. Additionally, as shown in results, the retrieved isolates in the current study displayed remarkable multidrug resistance to the majority of tested antimicrobial classes, including cefepime, ceftazidime, colistin, imipenem, meropenem, amikacin, ceftazidime, gentamicin, piperacillin, and tobramycin, while displaying high sensitivity to lipopeptides (colistin).

According to Jones, (2001), resistance patterns among nosocomial bacterial infections can change over time both within and between nations (Jones, 2001). Our investigation found that *P. aeruginosa* isolates were very sensitive to imipenem (94%), cefoperazone (71%), and amikacin (69%). This differs from the isolates from Bangalore (Veenakumari*et al.*, 2007) and Chandigarh

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(Taneja *et al.,* 2003) in terms of their antibiotic sensitivity pattern. *P. aeruginosa* exhibited 60–70% resistance to amikacin, ceftazidime, and ciprofloxacin in Bangalore research (Veenakumariet al., 2007). 42% of *P. aeruginosa* isolates in a Chandigarh investigation tested positive for imipenem resistance (Taneja *et al.,* 2003). Similarly, compared to the current study, *Acinetobacter* species demonstrated greater rates of resistance to ciprofloxacin, amikacin, ceftazidime, and pipercillin in a Bangalore investigation (Sinha *et al.,* 2007). We credit variations in the patient group studied by us for these variations in the susceptibility of strains.

Conclusion

The development of VAP is largely attributed to gram-negative bacilli, among which non-fermenters such *Acinetobacter baumannii* and *pseudomonas aeruginosa* are the most often isolated pathogens. Most Gram-negative bacteria that cause VAP are not very sensitive to antibiotics. Determining the risk factors associated with occurrences involving ventilators facilitates early detection and wise antimicrobial medication delivery, leading to a better outcome. In our healthcare system, late onset VAP is more common than early onset, however it is not substantially associated with higher mortality. The baseline VAP rate, risk factor, causal organism, and common medication susceptibility pattern shown in this study may be useful in improving the active monitoring program meant to accomplish an effective hospital infection control plan

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