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Original Research Article

VENTILATOR-ASSOCIATED PNEUMONIA IN MECHANICALLY VENTILATED PATIENTS: CLINICAL PROFILE, MICROBIOLOGICAL PATTERN, ANTIMICROBIAL RESISTANCE AND OUTCOMES IN A TERTIARY-CARE ICU

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is a serious complication in patients who are critically ill and require mechanical ventilation. The complications of VAP can increase the patient's morbidity and mortality. The increasing number of instances where multidrug resistant microorganisms occur makes its management more difficult and points out the necessity to know local patterns of microbiological and resistance data.

Materials and Methods: A prospective observational study was conducted over 15 months in the Medical Intensive Care Unit of Gandhi Medical College and associated hospitals, Bhopal. The research included 70 patients who underwent mechanical ventilation for 48 hours or more. Collection of data regarding demographic features, clinical features, presence of comorbidities, duration of mechanical ventilation, reintubation, sedation, and prior antibiotic use was done. Additionally, Glasgow Coma Scale, APACHE II score, and Clinical Pulmonary Infection Score were recorded for each patient. The endotracheal aspirate samples were processed for Gram staining, culture, and determination of antimicrobial susceptibility. The results were based on the assessment of patients in terms of survival and mortality.

Results: Among the 70 patients, 60% were male. The most prevalent comorbidities were hypertension (45.71%) and diabetes mellitus (40%). Cerebrovascular accident was the most common condition warranting the use of ventilatory assistance (41.43%). The endotracheal aspirate cultures were found to be positive in 88.57% of patients. The most common isolated organisms were Acinetobacter spp. (40.32%) followed by Klebsiella pneumoniae (22.58%) and Pseudomonas aeruginosa (14.52%). In general, 77.42% of isolated organisms were multi-drug resistant and 14.52% were pan-resistant. The overall mortality rate was calculated as 70%. Mortality in patients with APACHE II score >20, mechanical ventilation >10 days and positive culture results for listed variables was significantly higher (p=0.0004, p=0.003, p=0.047).

Conclusion: VAP is associated with a high prevalence of gram-negative multi-drug-resistant organisms and increased mortality in tertiary care medical ICU specifically Acinetobacter spp. emerged as the major infectious agent. In this setting, severity of illness, duration of mechanical ventilation and culture positivity were independent predictors of increased mortality. Outcomes in healthcare could be improved by paying attention to VAP prevention and early identification of high-risk patients as well as effective use of antimicrobials.

Keywords: Ventilator-associated pneumonia; multidrug resistance; Acinetobacter; antimicrobial resistance; APACHE II; intensive care unit.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is very common and severe infection in critically ill patients receiving invasive mechanical ventilation. VAP is primarily understood as pneumonia occurring more than 48 hours after the start of mechanical ventilation and endotracheal intubation.[1,2] The impact of VAP remains significant in ICUs even though the incidence reported varies greatly depending upon patient population, diagnostic definitions, duration of mechanical ventilation, and quality of infection prevention measures practiced.[3,4] The variations are especially notable in low-resource contexts where the practices in staffing, infrastructure development, infection control, as well as diagnostic capabilities may contribute towards VAP occurrence as well as its outcomes.

In India, tertiary-care ICUs continue to report a significant incidence of VAP, and studies have demonstrated variability in incidence, causative agents, as well as clinical outcomes.[5,6] The significance of VAP is not only in triggering a pulmonary infection. The management of patients with VAP may not only increase their time of mechanical ventilation but also prolong their hospital stay and utilization of health resources. Infections also bring a number of other complications. The mortality rate of patients with VAP has been found to depend on many factors, including severity of infection, etiological agents, antimicrobial susceptibility, timeliness and adequacy of treatment.[7,8] The discrepancies in rates are also due to individual particularities among patients, their diagnostic methods and particularities of treating VAP, which indicates importance of assessment of VAP in its own clinical conditions. [3,4] Etiological aspects of VAP are reliant on mechanical ventilation time, the usage of antimicrobial medications previously, colonization pressure, and local infection control methods. Early-onset VAP is seen with antibiotic-sensitive bacteria but late-onset conditions are usually associated with multidrug-resistant microbes.[6] Gram-negative species such as Acinetobacter, Pseudomonas aeruginosa, and Klebsiella pneumoniae are severe causes of VAP in numerous tertiary-care medical institutions. Indian studies reveal significant contribution of these germs and the high frequency of their resistance to antibiotics among VAP strains.[5,6] The rise of multidrug-resistant strains is a big problem due to the limiting therapeutic manoeuvres caused by high level of resistance against different types of medications that results in the risk of use of wrong medicines.[9,10] The question is even more pressing concerning patients of intensive care units, as they are treated by broad-spectrum antibiotics and stay in hospital for long periods of time. Thus, antimicrobial resistance in VAP is one of the important factors affecting effectiveness of therapy and outcomes of the disease.[9,11] The local antibiogram is a helpful tool for appropriately administering proven medications and modifying treatment in light of culture results. Furthermore, the spread of resistant Gram-negative species has emphasized the importance of microbiological confirmation and susceptibility testing in patients suspected of suffering from VAP.[9,11]

In this sense, knowledge of the local microbiological picture will help to develop useful treatment strategies not only on patient-specific basis, but also on the institutional level.

The causes and outcomes of VAP are numerous and depend on patient-related factors and some healthcare factors. Prolonged mechanical ventilation is one of the determinants, because the endotracheal tube negates any protective mechanisms of the upper airways, allowing for biofilm formation and aspiration of contaminated respiratory secretions. Among the factors described in the literature are advanced age, severe preexisting pathology, impaired consciousness, chronic pulmonary disease, sedation, supine position, improper oral hygiene and usage of broad-spectrum antibiotics.[12]

The greater severity of the disease itself, as well as the prolonged period of ventilatory support, can contribute to negative outcomes in patients diagnosed with VAP. Some clinical implications of this are prolonged dependence on the ventilator, longer stay in the Intensive Care Unit and higher mortality rates, especially if the causative infectious agent is an MDR organism or if a timely initiation of antibiotic therapy does not occur.[7,8]

However, diagnosing VAP is not an easy task due to the non-specific nature of the symptoms. The symptoms of fever, leucocytosis, purulent respiratory secretions and new or worsening visibility of pulmonary infiltrates can appear in many conditions typically seen in critically ill patients, such as atelectasis, pulmonary edema and ARDS, so doctors have to carefully analyse all the available information from clinical, radiological and microbiological points of view in order to be able to do diagnosis.[13] radiological tests, including endotracheal intubation and bronchoalveolar lavages, help doctors in the diagnosis of the organism by helping in the identification of the causative organism.[14] The difficulties of making the diagnosis together with the fact that the pathogens vary greatly and different forms of resistance are always possible mean that micro-biological characteristics, prevention and effectively manage VAP, infection-control practices, early diagnosis, microbiological evaluation, and the proper use of antibiotics must all be done together.

Preventive tactics that are based on scientific research should include the following: correct head-of-bed elevation, regular oral care, consistent assessment of whether the patient is ready to be weaned or is still sedated, prompt treatment of endotracheal secretions, along with timely reduction

or cancellation of unneeded mechanical ventilation.[15]

There are methods called care-bundles that have been created to enhance adherence to preventive measures in order to minimize the likelihood of developing VAP. Although, some factors like personnel levels, training, resources, and prevailing institutional practices can impede the implementation of these methods.[15] Moreover, the international guidelines refer to the necessity of proper microbiological evaluation and knowledge regarding antimicrobial sensitivity profile for a certain hospital.[16,17] However, substantial variability can still be seen in VAP microbiological profile, resistance patterns, and outcomes, despite the presence of preventive measures and treatment methods. Local data is helpful in offering useful insights into the common microbes, prevalence of AMR, as well as clinical factors responsible for the poor outcome of patients thus facilitating in making decisions about treating the disease in empiric way, stewardship of antibiotics, and preventing infection.

The present study was designed to assess VAP patients in a tertiary level ICU, regarding their clinical characteristics, the prevalence of microbes as well as AMR types and mortality rates.

MATERIALS AND METHODS

A prospective observational study was conducted in the Medical Intensive Care Unit (MICU) of the Department of Medicine, Gandhi Medical College and associated hospitals, Bhopal, over a period of 15 months. After getting the clearance from the Institutional Ethics Committee of Gandhi Medical College, Bhopal, written informed consent was obtained from every participant's legally authorized representative or attendant.

The study included 70 patients. The sample was estimated using an earlier reported prevalence of 18% of VAP in India at 95% confidence level (Z=1.96) and an allowed margin of error of 9%, yielding a sample size of 70 patients. The study participants included those who met the inclusion criteria and gave consent to participate in the study.

The inclusion criteria consisted of individuals who were over 18 years of age, admitted to the MICU, required mechanical ventilation for more than 48 hours and did not have pneumonia at the time of entrance to the MICU. Those who were admitted with community-acquired pneumonia, chronic obstructive pulmonary disease, bronchiectasis or other chronic respiratory pathology, active pulmonary tuberculosis and valvular heart diseases or infective endocarditis or who required mechanical ventilation for less than 48 hours and those who refused to give consent were excluded.

After enrolment, all demographic and clinical data were recorded, and baseline tests were conducted. These tests consisted of complete blood cell count, chest x-ray, renal function tests, liver function tests, serum electrolytes, C-reactive protein, and routine urinalysis tests. Every participant was evaluated daily for VAP using the Clinical Pulmonary Infection Score (CPIS). The CPIS included taking temperature, blood leukocyte count, quantity of tracheal secretions, number of radiographic infiltrates seen on chest x-ray, and the PaO_2/FiO_2 ratio.

Aspiration samples were obtained from participants safely and sent straight to the microbiology laboratory. The samples underwent gram staining, culture, and sensitivity testing to determine pathogens. Clinical progress was monitored until patients were discharged or passed away, and the clinical findings and CPIS score were recorded for all patients. The outcome was measured in terms of mortality among VAP patients.

For categorical variables, frequencies (% values) were used, and comparisons were made with Pearson's chi-square test. Continuous variables were shown by using mean ± standard deviation and comparisons were made using a t -test for comparing any two means.

Statistical analysis was performed using SPSS version 20, and a p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline characteristics of patients (n=70)

Characteristic	n (%)
Male	42 (60.0)
Female	28 (40.0)
Hypertension	32 (45.7)
Diabetes mellitus	28 (40.0)
Obesity	15 (21.4)
Chronic kidney disease	11 (15.7)
Cerebrovascular accident	29 (41.4)
No comorbidity	24 (34.29)

The study comprised a total of 70 patients. The average age of the patients was 46.07 ± 10.42 years. Most of the patients were males, 60.0% to be exact. The patients had health problems like hypertension diabetes mellitus, obesity and chronic kidney disease.

Hypertension was seen in 45.71% of the patient's diabetes mellitus in 40%, obesity in 21.43% and

chronic kidney disease in 15.71%. One-third of the patients did not have any health problems.

Table 2: Clinical Profile

Parameter	n (%)
Mechanical ventilation >10 days	18 (25.7)
Sedative use	48 (68.6)
Prior antibiotic use	29 (41.4)
Reintubation	24 (34.3)
APACHE II >20	36 (51.4)
CPIS >7	50 (71.4)

The mean duration of mechanical ventilation was 8.06 ± 4.17 days. The time spent on mechanical ventilation was 6-10 days (42.86%), while 25.71% spent more than 10 days on mechanical ventilation. The history of addiction was noted in 44.29% of patients.

Re-intubation was done in 34.29% of patients while 68.57% were sedated and 41.43% had been given antibiotics. The majority of patients had difficulty in consciousness, where 48.57% of them were scored 6-8 on Glasgow Coma Scale (GCS). More than half of the patients had an APACHE II score of more than 20.

Table 3: Microbiological profile of culture-positive isolates (n=62)

Organism	n (%)
Acinetobacter spp.	25 (40.3)
Klebsiella pneumoniae	14 (22.6)
Pseudomonas aeruginosa	9 (14.5)
Escherichia coli	4 (6.5)
Enterobacter spp.	3 (4.8)
Citrobacter spp.	2 (3.2)
Polymicrobial infection	5 (8.1)

Endotracheal aspirate cultures were positive in 62 (88.57%) patients and negative in 8 (11.43%). Among the culture-positive samples, Acinetobacter spp. was the predominant isolate (40.32%), followed by Klebsiella pneumoniae (22.58%) and Pseudomonas aeruginosa (14.52%). Escherichia coli, Enterobacter spp. and Citrobacter spp. accounted for 6.45%, 4.84% and 3.23%, respectively. Polymicrobial infections were identified in 8.06% of culture-positive cases.

Table 4: Antimicrobial resistance pattern

Antibiotic	Resistant, n (%)
Ceftriaxone	55 (88.7)
Amoxicillin-clavulanate	54 (87.1)
Ceftazidime	53 (85.5)
Ciprofloxacin	52 (83.9)
Cefotaxime	51 (82.3)
Piperacillin-tazobactam	48 (77.4)
Meropenem	33 (53.2)
Imipenem	30 (48.4)

Antimicrobial susceptibility testing demonstrated high levels of resistance among culture-positive isolates. Resistance was highest to ceftriaxone (88.71%), amoxicillin-clavulanate (87.10%), ceftazidime (85.48%), ciprofloxacin (83.87%) and cefotaxime (82.26%). Resistance to piperacillin-tazobactam, cotrimoxazole, gentamicin and amikacin was 77.42%, 79.03%, 74.19% and 70.97%, respectively. Carbapenem resistance was also substantial, with resistance to meropenem and imipenem reported in 53.23% and 48.39% of isolates, respectively.

Table 5: MDR status and outcome

Outcome	n (%)
MDR isolates	48/62 (77.4)
Non-MDR isolates	14/62 (22.6)
Death	49/70 (70.0)
Survived	21/70 (30.0)

Out of 62 patients whose culture results were positive, 48 (77.42%) were found to be multi-drug resistant. The total mortality rate in the cohort was 70.0% (49 out of 70 patients).

Table 6: Factors associated with mortality

Factor	Mortality	*p*-value
APACHE II >20	32/36 (88.9%)	0.0004
Mechanical ventilation >10 days	17/18 (94.4%)	0.003
Culture positive	46/62 (74.2%)	0.047

Mortality rates increased significantly with higher APACHE II scores, going from 25.00% for patients with scores of 10 or less to 57.69% for patients scoring between 11 and 20 and 88.89% in patients with scores greater than 20 (p=0.0004). It increased further based on the duration of mechanical ventilation, as mortality rate increased from 45.45% for non-invasive ventilation for less than or equal to 5 days to a rate of 73.33% for 6–10 days and a rate of 94.44% for greater than 10 days of mechanical ventilation (p=0.003). Patients who had positive culture results also had higher mortality rates than patients with negative cultures (74.19% vs 37.50%; p=0.047; OR=4.79).

DISCUSSION

The current research assessed the ventilator-dependent patients that had been diagnosed with ventilator-associated pneumonia in an advanced care intensive care unit characterizing them with high rate of severe condition, Gram-negative bacteria infection, drug resistance and death. The average age of the sample was 46.07 ± 10.42 years, where males constituted the majority (60%). The top two comorbidities were high blood pressure and diabetes while stroke was the primary diagnosis for those admitted. Over fifty percent of the sample had their APACHE II scores more than twenty, and about three quarters had their CPIS exceeding seven implying that the sample belongs to the high-risk population. Special importance is given to the development of VAP in patients treated in ICUs as a result of mechanical ventilation which enables bypassing of natural protective barriers and allowing for micro-aspiration, colonization and biofilm forming in the tube used for ventilation operation.[1]

Numerous accepted risk factors for VAP were often found in this study. Sedative medication was used by 68.57% of patients, reintubation occurred in 34.29%, previous antibiotic therapy had been given to 41.43% of patients, and a fourth of the patients were treated with mechanical ventilation lasting longer than 10 days. Prolonged mechanical ventilation is of special significance since the risk of VAP increases with the duration of the endotracheal tube use.[6] The influence of previous antibiotic administration is due to the fact that it may change the composition of microorganisms present in the respiratory tract due to the higher likelihood of the resistant microorganisms' development.[11] Ochoa and his colleagues performed a systematic review consisting of meta-analysis proving that the length of mechanical ventilation is one of the important factors concerning VAP therapy.[6] Likewise it has been shown that there is a correlation between VAP and prolonged mechanical ventilation, reintubation, and other risk factors mentioned in Indian studies.[7]

Positive endotracheal aspirate cultures were observed in 88.57% of patients in the current study. The study results showed that in most cases gram-negative organisms were found, with Acinetobacter spp. found in 40.32%, followed by Klebsiella pneumoniae (22.58%) and Pseudomonas aeruginosa (14.52%). Although gram-negative bacilli have been shown to prevail in cases of VAP, the proportion of every pathogen may differ depending on the geographical region, specifics of ICU, patient population and local antimicrobial regimen.[2] Survey studies conducted in India show the prevalence of Acinetobacter, Pseudomonas and Klebsiella among pathogens found in the cases of VAP.[7] Golia et al. have also shown that gram-negative organisms are often found in both early-onset and late-onset VAP in a tertiary care ICU in India.[9] Acinetobacter showed a significant amount of presence in the current study and an important clinical aspect of this finding is that it is often associated with high levels of drug resistant bacteria and can play an important role in limiting treatment options.[11]

The findings regarding antimicrobial susceptibility produced strong evidence of the magnitude of the resistance problem itself. Of the culture-positive isolates, 77.42% turned out to be multidrug resistant, while the highest resistance was found to be with respect to ceftriaxone (88.71%), amoxicillin-clavulanate (87.10%), ceftazidime (85.48%), ciprofloxacin (83.87%), and cefotaxime (82.26%). Resistance to piperacillin-tazobactam and carbapenems was also found to be high. The observed high resistance to commonly used antimicrobial drugs is worrisome, as the empirical treatment of VAP usually requires the use of broad-spectrum antibiotics and in case of inappropriate initial therapy there are negative consequences.[11] The multiple causes behind the emergence of antimicrobial resistance include antimicrobial drug exposure, transmission in health services, and selective pressure in ICUs.[12] It has recently become clear that controlling antimicrobial use in the ICU, monitoring drug pathologies and discovery of novel cure options for resistant Gram-negative infections have been very vital.[13]

The high levels of antimicrobial resistance shown in the current study further highlights value of local antibiograms. Even though global guidelines suggests how to manage hospital-acquired and ventilator-associated pneumonia empirically, the selection of the antibiotic should be based upon the local occurrence and susceptibility of pathogens.[17] Bassetti et al. pointed out the growing difficulty to manage the infection by multidrug resistant forms of hospital-acquired and ventilator-associated pneumonia more effectively by properly selecting appropriate antibiotics.[13] In the current case, frequent resistances of frequently used antibiotics suggest the need to reassess the empirical treatment protocols in accordance with local microbiological data, followed by de-escalation where relevant.[17]

The diagnosis of VAP is complex, as symptoms such as fever, leucocytosis, purulent respiratory secretions, and radiological infiltrates may occur in other illnesses among critically ill patients. The

current study used clinical assessment in conjunction with CPIS and an endotracheal aspirate culture for diagnosis. Most patients had a CPIS score of over seven, which indicated a high likelihood of infection. Nonetheless, it is important to obtain microbiological confirmation to determine the pathogen and ensure that the right antibiotic treatment is prescribed. In a study by Corrêa et al., the use of quantitative cultures of endotracheal aspirates and bronchoalveolar lavages showed evidence of the usefulness of microbiology in VAP management.[15] However, the limitations of clinical scores and microbiological methods should be noted, since no single approach is perfect in terms of sensitivity and specificity.[14]

In the current research, the rate of death was shown to be 70%, which highlights the tremendous effect of VAP on the critically ill group of patients. The mortality rate for the VAP varies a lot between studies due to dissimilarities in patients' traits, patient illnesses, severity of illnesses in the patients, organisms that caused the diseases, resistance to medicines by microbes, and routine practices in ICUs.[3] The contribution of nosocomial pneumonia to the mortality of patients in the intensive care unit was confirmed by Fagon et al.[5] In the current research, the high mortality level was due, at least partly, to the fact that patients had severe illnesses prior to coming to the researchers and a high occurrence rate of such diseases as multi-drug-resistant infections, as well as the dependence on ventilators for a long period of time.

One of the most important conclusions that can be drawn is the close relationship between severity of disease and mortality. Significantly, mortality rates increased if higher values of APACHE II score are attained, and patients with the score >20 have 88.89% mortality rates. Thus, this confirms the statement of the importance of timely identification of patients with severe derangement of physiology as well as high chances of negative outcomes.[5]

The situation concerning the severity of the disease and its VAP-related consequences has already been described by previous works.[5] However, it should be mentioned that, while analysing the severity of the disease, it should be considered that the factors related to the course of the disease do not matter a important give that the disease' assessment should be first done taking into consideration the severity of the previous condition.

As for the current study, the analysis also disclosed a correlation between the length of duration of mechanical ventilation and mortality rate among patients.[6]

This research shows that the high death rate and resistance level necessitates the vital role of prevention in the management of the disease along with treatment. The prevention of VAP should aim at creating conditions that minimize unnecessary exposure to ventilators and increasing the compliance of practices that were documented in evidence-based sources. The work of Rello et al. showed the purposefulness of using bundles of solutions to ensure compliance with preventive measures and reduce the risk of VAP.[16] As a result, a coordinated approach to implementing preventive measures should be taken rather than applying scattered techniques alone. Appropriate hand hygiene, oral care, head-of-bed elevation, assessment of sedation and readiness to be released from ventilators, as well as avoidance of unnecessary reintubation are all key elements of an efficient approach to prevention.[16] All in all, the observations made in this paper prove that VAP in this level 3 hospital was characterized by a large number of Gram-negative microorganisms, the presence of Mult-resistant organisms, and a high death rate. It has also been confirmed that APACHE II scores and time spent on mechanical ventilation play a significant role in death rates. The results support the necessity for an integrated plan that includes early identification of patients at high risk, microbiological assessment methods, local resistance monitoring, reasonable antimicrobial medical practices, and antimicrobial management practices.

Overall, the findings of the present study indicate that VAP in this tertiary-care ICU was associated with a predominantly Gram-negative microbiological profile, a high prevalence of MDR organisms and substantial mortality. The significant association of mortality with APACHE II score and duration of mechanical ventilation suggests that both severity of illness and prolonged ventilator dependence are important determinants of outcome. These findings reinforce the need for a combined strategy involving early recognition of high-risk patients, appropriate microbiological evaluation, local resistance surveillance, rational antimicrobial therapy, antimicrobial stewardship and consistent implementation of VAP prevention bundles.[11]

Limitations: This study was limited to one centre, which restricts its findings. Diagnosis depended entirely on CPIS, which is not fully reliable regarding its specificity, with bronchoalveolar lavage and other advanced diagnostics unavailable for this study. Observations were not enough for statistical purposes.

CONCLUSION

As shown by the study, there is a significant prevalence of drug-resistant pathogens among patients on ventilators, among which Acinetobacter spp. were most common, followed by Klebsiella pneumoniae and Pseudomonas aeruginosa. At the same time, the resistance to treatment was significant and the mortality rate reached 70%. Additionally, APACHE II scores and the time on mechanical ventilation had a significant correlation with the death rate.

Recommendations

The setting of the study should concentrate on improving the compliance with VAP prevention bundles in the institution so that much attention can be paid to hand hygiene, oral care, the right position, sedation minimization, and trying to assess the patient on a daily basis whether he/she can be weaned off the ventilator. Obtaining microbiological tests on a routine basis and compiling an antibiogram specific to the Intensive Care Unit will help make the right choice when it comes to choosing antibiotics, as this will allow using antibiotic therapy based on culture results. There should be an increase in the implementation of antimicrobial stewardship programs to avoid the use of broad-spectrum antibiotics in unnecessary situations and minimize the possibility of emergence of multidrug-resistant organisms. Additionally, certain patient categories, including the ones suffering from severe APACHE II scores and patients using mechanical ventilators for a long period of time, should be monitored for identifying the signs of deterioration as soon as possible.

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