ORIGINAL RESEARCH PAPER

A STUDY OF BACTERIAL PATTERN OF VENTILATOR ASSOCIATED PNEUMONIA AT A TERTIARY CARE CENTRE OF WESTERN INDIA

General Medicine

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ABSTRACT

Background: Ventilator associated pneumonia (VAP) remains the commonest co-morbid infection in patients admitted to ICU leading to increased morbidity and mortality, despite the technological advancements in health care. Hence, a study of the local bacterial pattern of VAP along with antibiotic sensitivity is essential to frame institutional antibiograms to ensure appropriate empirical treatment of VAP.

Aim: The present study aims to study the bacterial pattern of VAP in medical ICUs in a tertiary care center along with the antibiotic sensitivity of the isolates.

Method: A descriptive, observational, cross-sectional study was conducted in combined 45 bedded, medical ICUs, at Sawai Man Singh Medical College and Hospital, from March 2020 to 2021. A total of 105 cases were enrolled after application of appropriate exclusion and inclusion criteria from patients on mechanical ventilation for > 48 hours without prior evidence of pneumonia or sepsis. Data regarding demographic and clinical features, laboratory parameters, culture and sensitivity and outcome in terms of death or discharge were collected in a pre-structured proforma and analyzed.

Results: Out of the 105 patients evaluated in the study, 71(67.6%) were males. The mean age of the study population was 45.1 years (45.1 17.57) with a range of 18-85 years. Majority were below the age of 40 years (46.7%) followed by those above 60 years (26.7%). The incidence of VAP in the study was 49.5%. Most common co-morbidities underlying patients of VAP was chronic obstructive pulmonary disease (14.3%), coronary artery disease (13.3%), and chronic kidney disease (10.5%). Patients of VAP had a mean temperature of 101.1F (Mean ± SD; 101.1 0.99), along with leukocytosis (Mean ± SD;14399 5373), elevated serum creatinine (Mean ± SD; 1.9 5.9), alanine aminotransferase (Mean ± SD; 84.4 153.7), aspartate aminotransferase (Mean ± SD; 128.7 238.4), and LDH (Mean ± SD; 861.6 690.2), and decreased serum albumin(Mean ± SD; 3.0 0.5). The predominant isolate from endotracheal aspirate culture was *Enterobacter* species (17.2%), followed by *Pseudomonas* (15.2), *Klebsiella* (6.7%), *Acinetobacter* species (6.7%), and *E. coli* (4.9%). Those isolated from blood were *Enterobacter* species (17.2%), followed by *Pseudomonas* (6.7%), *Klebsiella* (6.7%), *Enterococcus* species (5.7%), and coagulase positive *S.aureus* (5.7%). The antibiotic sensitivity in the study revealed sensitivity predominantly to polymyxin (57.9%) and tigecycline (52.6%) followed by piperacillin-tazobactam (47.4%) and aztreonam (23.7%). The mortality in the study was 46.7%.

Conclusion: The incidence of VAP in our study was 49.5% attributed to the use of microbiological definition to select cases of VAP and to lack of adequate nursing staff. Most of the isolated organisms isolated from endotracheal aspirate were multidrug resistant organisms sensitive to polymyxin and tigecycline. The mortality observed was also high due to prevalence of multi drug resistance and polymicrobial infection and delay in institution of appropriate antibiotics. Large multicentric studies with large sample size are needed to study the risk factors and their relation in causation of VAP.

INTRODUCTION:

Nosocomial infections are the major cause of morbidity and mortality in intensive care units (ICUs) and this is a big dogma that the health care facilities face today. The incidence of nosocomial infections in ICUs is 2-5 times higher than in a general health care setting[1]. Pneumonias account for second most common intensive care acquired infection and 86% of them are ventilator associated pneumonias (VAP)[2]. VAP is the most common morbid hospital acquired infection, and the gravity of the situation further intensifies due to the prevalence of multi drug resistant and extended drug resistant organisms. Thus, the study of microbial pattern of VAP along with drug sensitivity pattern is essential for health care institutes to ensure judicious use of antimicrobials and to reduce the morbidity and mortality associated with VAP.

VAP is defined as nosocomial pneumonia that develops in individuals 48 hours after mechanical ventilation by either endotracheal intubation or tracheostomy[3]. Despite use of sepsis care bundle and ventilator care bundle the incidence of VAP is about 10-20% in patients on mechanical ventilation (MV) for more than 48 hours[4]. VAP is associated with varying mortality rates, ranging from 24- 50% which can sometimes be as high as 76%[5]. It is also the major cause of prolonged hospitalization, increased cost of health care and increased burden on the limited health care infrastructure available. Several studies have shown that clinical criteria to diagnose VAP have often been imperfect, and their diagnostic reliability has been dubious, hence additional procedures to accurately establish the diagnosis like culture of organism from lower respiratory tract aspirate are required.

Studies world over have shown that early diagnosis and appropriate antimicrobial selection plays a pragmatic role in management of VAP. The pattern of organisms causing VAP varies with type of study population and types of ICUs. Hence, it is essential to study the bacterial pattern of VAP in ICUs in tertiary care centers and establish an antibiogram, to ensure judicious use of antimicrobials and for effective management of VAP. Thus, this study aims to study the bacterial pattern of VAP in ICUs at a tertiary care center along with the culture and sensitivity in relation to the clinical and demographic features of the study population.

METHODS:

This observational descriptive cross-sectional study was conducted at combined medical ICUs of Sawai Man Singh Medical College and attached group of hospitals with a capacity of 45 beds, over a period of one year from March 2020 to March 2021. The study was approved by the institutional ethics committee. The patients admitted during this period, requiring mechanical ventilation were included after application of appropriate inclusion and exclusion criteria. Adult patients without evidence of sepsis, pneumonia, or multi organ dysfunction (MODS) within 48 hours of admission to ICU, having microbiologically confirmed VAP 48 hours after admission to ICU were included in the study after written informed consent. VAP in the study is defined microbiologically as cases having positive endotracheal aspirate culture. Fever is defined as rise in the core body temperature of 1C and a core temperature of > 38.5C.

Data regarding demographic variables, clinical features, underlying co-morbidities, routine laboratory investigations, arterial blood gas analysis (ABG), tracheal aspirate culture and sensitivity and blood cultures, number of days of stay in the ICU as well as the outcome of the patient in terms of death or discharge were collected in a pre-structured proforma. Written informed consent was taken from the attendants of the patients enrolled in the study. All procedures for data collected were kept confidential according to Helsinki declaration of biomedical ethics. Data was collected at the time of admission and 48 hours after admission to ICU. Endotracheal aspirates were taken under complete aseptic precautions and sent to microbiology lab for gram's staining and culture and drug sensitivity after 48 hours of being on mechanical ventilation. The antibiotic sensitivity test was done by Modified Kirby Bauer Disc Diffusion method.

The proforma was then screened for errors and completeness of data. The data was then entered in Microsoft excel sheet and analyzed. After entry of data of every 10 proformas, one random proforma was picked and data entry was rechecked. Also, an independent individual verified data entry of two randomly picked proformas, after every 15th questionnaire was entered. Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). Univariate analysis was done, and results were presented in form of tables and bar diagrams. Descriptive statistics were used to calculate frequencies of categorical variables. Continuous data was expressed as mean and standard deviation and categorical variables were expressed as percentages. Independent t-test and ANOVA test were used to compare continuous variables and Chi-square test was used for categorical variables. Data were summarized using median and standard deviation for quantitative variables and percentage and frequency for qualitative variables. Non- parametric Mann Whitney test and Kruskal Wallis test were used for data that did not follow normal distribution. A p-value of < 0.05 was considered statistically significant.

RESULTS

The study enrolled a total of 105 patients after appropriate application of inclusion and exclusion criteria. Among the 105 patients included in the study 52 patients (49.5%) had microbiologically confirmed and culturally significant VAP. Hence, the incidence of microbiologically significant VAP in the study was 49.5% (Figure.1).
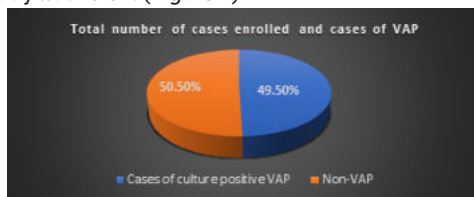

Figure. 1 Total number of cases of VAP and Non-VAP

Males (71) predominated the study population at 67.6% as compared to females (32.4%). The age distribution of the population revealed that, most of the patients were < 40 years accounting for 46.7% of the patients and the next most common age group was that of elderly > 60 years comprising of 26.7% of the patients. Among the rest 14.3% were in the age group 41-50 years and 12.4% were in the age group 51-60 years. The mean age of the study population was 45.1 years (45.1±17.57), with a range of 18-85 years (Table.1).

Table 1. Age and Sex distribution of the study population

Variable	(n) Percentage
SEX	
MALE	71 (67.6%)
FEMALE	34 (32.4%)
AGE GROUPS	
UPTO 30 years	27 (25.7%)
31-40 years	22 (21%)
41-50 years	15 (14.3%)
51-60 ears	13 (12.4%)
>60 years	28 (26.7%)

The commonest co-morbidities observed in the study population were chronic obstructive airway disease (COPD; 14.3%), coronary artery disease (CAD; 13.3%) and chronic kidney disease (CKD; 10.5%) followed by cerebrovascular accident (CVA; 7.6%), diabetes mellitus (DM; 6.7%), hypertension (5.7%), chronic liver disease (CLD; 4.8%), meningitis (2.9%) and poisoning (1.9%) (Figure.2).
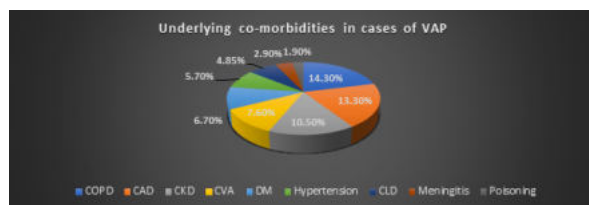

Figure. 2 Underlying co-morbidities in cases of VAP

Temperature profile of the patients revealed that, the mean temperature at time of admission to ICU was 98.6 F(98.6 1.12) and the mean temperature 48 hours after admission was 101.1F (101.1 0.99). The hemogram of study population observed had significant leukocytosis with neutrophilia with rest of the hemogram being within normal range. The mean leucocyte count of the patients was 14, 399 cells/mm^3 (14399 5373). The hemogram also had significantly elevated erythrocyte sedimentation rate (ESR) with a mean of 46.7 (46.7 21.7). Study of biochemical parameters revealed that renal and liver functions were deranged, and the study population also had hypoalbuminemia and elevated lactate dehydrogenase (LDH). The mean value of blood urea and serum creatinine was 44.2 mg/dL (44.2 30.3) and 1.9 mg/dL (1.9 5.9), respectively. The mean value of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was 84.4 IU/L (84.4 153.7) and 128.7 IU/L (128.7 238.4), respectively. The mean value of serum albumin and serum LDH in the study was 3.0 mg/dL (3.0 0.5) and 861.6 IU/L (861.6 690.2), respectively (Table.2).

In the analysis of arterial blood gases of patients, it was observed that mean pH was 7.36 (7.36 0.73), mean PaO2 was 124 mmHg (124.0 53.01), and mean FiO2 was 77.9% (77.9 16.95). Also, the mean value of serum lactate was elevated and observed to be 2.24 mmol/L (2.24 1.80) (Table.2).

Table. 2 Clinical, Laboratory and Arterial blood gas parameters in patients of VAP

Variables	Mean	Standard deviation
Temperature at admission(F)	98.6	1.12
Temperature 48 hours post admission(F)	101.1	0.99
HEMATOLOGICAL PARAMETERS		

Hemoglobin (gm/dL)	12.4	10.64
Total leucocyte count (cells/mm^3)	14,399	5,373
Neutrophils (%)	81.3	7.35
Lymphocytes (%)	11.6	4.80
Platelets (lakhs/mm^3)	1.9	0.85
ESR	46.7	21.70
Blood Urea (mg/dL)	44.2	30.32
Serum Creatinine (mg/dL)	1.9	5.98
Alanine aminotransferase (ALT) (IU/L)	84.4	153.70
Aspartate aminotransferase (AST) (IU/L)	128.7	238.40
	3.0	0.54
Serum albumin (mg/dL)	861.6	690.22
LDH (IU/L)		
ARTERIAL BLOOD GAS PARAMETERS		
pH	7.36	0.73
PaO2 (mmHg)	124.0	53.01
FiO2 (%)	77.9	16.95
Serum lactate (mmol/L)	2.24	1.80

The culture of endotracheal aspirate showed that about 46 (43.8%) had no growth on culture and 56.2% had growth on culture. The commonest isolates were *Enterobacter* species (17.2%), *Pseudomonas* (15.2%), *Klebsiella* (6.7%), *Acinetobacter* species (6.7%), and *E.coli* (4.9%). The rest of the isolates were coagulase positive *Staphylococcus aureus* (1.9%), coagulase negative *S.aureus* (1%), *Citrobacter* species (1%), *Diphtheroids* (1%), and few commensals (1%). No isolates were obtained from 47.6 % of the patients on blood culture from peripheral line. The major isolates from blood culture of the study population were *Enterobacter* species (17.2%), *Klebsiella* (6.7%), *Psuedomonas* (6.7%), *Enterococcus* species (5.7%), and coagulase positive *S.aureus* (5.7%). The rest of the isolates were *Acinetobacter* species (3.8%), *Citrobacter* species (2.9%), coagulase negative *S.aureus* (2.9%), and *E.coli* (1%) (Figure.3).
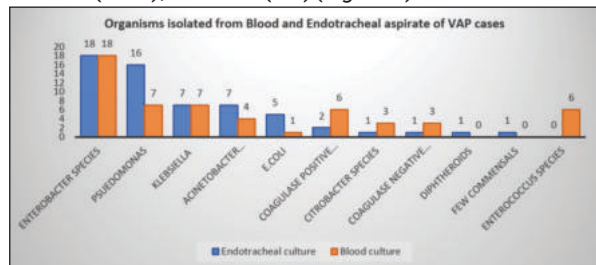

Figure. 3 Blood and Endotracheal aspirate cultures from patients of VAP

The antimicrobial sensitivity of organisms isolated from endotracheal aspirate and blood cultures of patients of VAP, revealed them to be predominantly sensitive to Polymyxin (57.9%), Tigecycline (52.6%), Piperacillin-tazobactum (47.4%) and Aztreonam (23.7%). Sensitivity was also seen to few other antibiotics namely, Gentamycin (21.1%), Linezolid (18.4%), Cefoperazone (18.4%), Colistin (15.8%), Teicoplanin (15.8%), Cotrimoxazole (13.2%), Vancomycin (13.2%), Cefepime (7.9%), Amikacin (7.9%), and Ceftazidime (5.3%) (Figure.4).
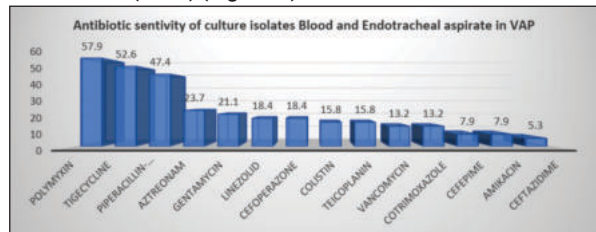

Figure. 4 Antibiotic sensitivity of the Blood and endotracheal aspirate isolates in patients of VAP

In the present study, the mean duration of stay in the ICU was 18.57 days (Mean ☐ SD; 18.57 ☐ 8.61) and the median was 18 days. The range of length of stay in ICU was from a minimum of

5 days to a maximum of 42 days. Out of 105 patients enrolled, 49 (46.7%) died and 54 (51.4%) were discharged and 2 left against medical advice (Figure.5).
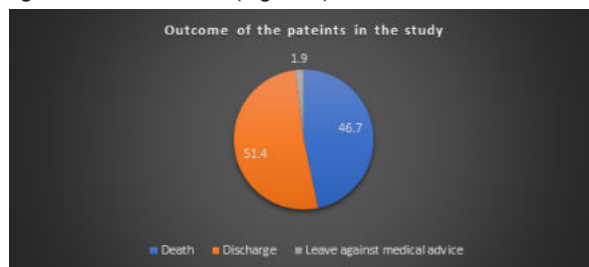

Figure. 5 Outcome of the study population

DISCUSSION
The present study was conducted at combined medical ICUs at a tertiary care center over a period of one year to study microbial and antimicrobial sensitivity pattern of prevalent organisms causing VAP. VAP is major cause of morbidity, mortality, increased length of hospital stays, and increased cost of health care which is further magnified by prevalence of multi drug resistance. Hence, a study of this kind is essential to establish an antibiogram for the health care institutes as per the prevalent flora to decrease the morbidity, mortality and burden on health care infrastructure related to VAP in ICUs.

The incidence of microbiologically confirmed VAP in the present study is 49.5%, in studies across the globe the incidence varies from 15-58%[6]. The incidence of VAP varies with the studied population, type of institute, the definition used to define VAP, application of infection control programs for prevention of nosocomial infections, and the income level of the country. The higher incidence in our study is due to the fact that all cases of MV of duration of > 48 hours showing growth in culture of endotracheal aspirate, irrespective of clinical criteria for VAP being satisfied or not, were included in the study. The other reason for the higher incidence, could also be, understaffing of ICUs. Low staff to patient ratio in ICUs lead to lapse in aseptic precautions and over burden deteriorates the quality of health care imparted. In another study of mechanically ventilated patients in ICU, at a tertiary care center, from Lebanon the incidence of VAP was estimated at 47%[7]. In a study of 427 mechanically ventilated patients, at pediatric ICU (PICU) in Cairo, Egypt incidence was estimated at 31%[8]. In a 30-month prospective study, from Saudi Arabia the incidence of VAP was 10.3%[9]. Thus, incidence varies widely in studies across the globe depending on several factors.

Our study had a male sex (67.6%) preponderance for VAP. The predominant age- groups affected by VAP in our study were those of individuals aged < 40 years (46.7%) and > 60 years (26.7%). This fact may be due to overall preponderance of male sex for admission to intensive care unit. The major co-morbidities in the current study population were COPD (14.3%), CAD (13.3%), and CKD (10.5%). Majority of patients developed fever after admission to ICU and mechanical ventilation with a mean temperature of 38.4C (38.4 0.99). The hematological parameters of the study population revealed leukocytosis (Mean SD; 14399 5372) indicative of infection thus clinically supporting diagnosis of VAP. The biochemical parameters like serum creatinine (Mean SD; 1.9 5.9), aspartate aminotransferase (Mean SD; 128.7 238.4), alanine aminotransferase (Mean SD; 84.4 153.7) and LDH (Mean SD; 861.6 690.2) were elevated, which are again indicative of infection.

In the study, microbial growth from culture of endotracheal aspirates was seen in 56.2% of the study population. The isolated organisms included *Acinetobacter* species, *Psuedomonas, Enterobacter* species, *E.coli, Klebsiella, Citrobacter* species, Coagulase positive *Staphylococcus*,

Coagulase negative *Staphylococcus*, *Diphtheroids* and few commensals. The predominant organism in our study was *Enterobacter* species (17.18%), followed by *Psuedomonas* (15.2%), *Klebsiella* (6.7%), *Acinetobacter* (6.7%) and *E.coli* (4.9%). Studies across the globe reveal *Pseudomonas* and *Acinetobacter* to be predominant isolates from endotracheal aspirates. But their presence merely suggests colonization and doesn't necessarily mean infection. Hence, it is very difficult to assess true frequency of infection caused by them. The isolates from our study were similar to studies by Alexis M Elwald et al[10] (2002, St. Louis), Patra PK et al[11] (2007, PGI, India) and Vedavathy S et al[12] (2009, Bangalore, India); where too the most common pathogens isolated were Pseudomonas and Klebsiella. A study by Centre for Disease Control, USA, including 8474 cases of VAP from 2009-2010, the most common organisms isolated were *S. aureus* (24.1%), *P. aeruginosa*(16.6%), *Klebsiella* species (10.1%), *Enterobacter* species (8.6%), *Acinetobacter baumannii* (6.6%), and *E. coli* (5.9%)[13]. Another study from University of North Carolina Hospital, over a period of 4 years evaluated 158,519 patients; and amongst them 327 developed VAP, with the infecting flora comprising of methicillin-susceptible *S. aureus* (MSSA; 9%), methicillin-resistant *S. aureus*(MRSA; 18%), *P. aeruginosa* (18%), *Stenotrophomonas maltophilia* (7%), *Acinetobacter* species (8%), and other species (9%)[14]. This variation in the predominating organisms is due to variation in the study population, type of ICU, and application of infection control measures. However, studies world over, show a higher prevalence of gram-negative organisms in patients of VAP.

Blood cultures done in the study participants were positive in 52.4% cases. The common isolated organism being *Enterobacter*species (17.2%), followed by *Klebsiella* and *Pseudomonas* with 6.7% each. The rest include *Enterococcus* species (5.7%), coagulase positive *S.aureus* (5.7%), *Acinetobacter* species (3.8%), *Citrobacter* species (2.9%), coagulase negative *S.aureus* (2.9%), and *E.coli* (1%).

The antibiotic sensitivity pattern in the present study, highlighted the higher prevalence of multi-drug resistant organisms. The most common risk factors for prevalence of MDR pathogens in any setting are prolonged hospitalization and recent exposure to antibiotics. Thus, one begets the other. In our study, majority of organisms were found to be sensitive to Polymyxin (57.9%), Tigecycline (52.6%), and Piperacillin and tazobactam (47.4%). The other antibiotics that the organisms were sensitive to included Aztreonam, Gentamycin, Linezolid, Cefoperazone, Teicoplanin, Colistin, Vancomycin, and Cotrimoxazole. The higher prevalence of multi-drug resistant (MDR) and extensively drug resistant (XDR) organisms mandates a thorough knowledge of the prevalent antimicrobial resistance in an institute for the appropriate initiation of empirical antibiotic therapy. Thereby, curbing down the length of stay in hospital and giving better outcomes in patients of VAP. All institute must thus, have a knowledge of prevalent common pathogens and their antibiotic susceptibility. An antibiogram must be formulated accordingly with periodic upgradation and dispersed to different units in the hospital.

Patients with VAP have 2-10 times higher mortality and increased morbidity when compared to patients on mechanical ventilation without VAP[15]. The mortality rates associated with VAP are highly variable ranging from 20-50% across different study populations and institutes[16]. The overall mortality in our study was observed to be 46.7%. This high mortality could be attributed to underlying co-morbid conditions in majority of the patients evaluated in the study and to the delay in institution of effective empirical antimicrobials. The results from our study are similar to the study by Mukhopadhyay et al.[17], in which the overall mortality attributed to VAP was 47.3%. Ramya et al.,[18] and Alexis et al.,[19] too reported similar high mortality rates amongst cases of VAP. In our study patients of VAP had a prolonged duration of

ICU stay (Mean SD; 18.57 8.6) and morbidity. The results are similar to study by Khalid Amro et al.,[20] and Patra PK et al[10]. Thus, VAP increases duration of hospital stay, thereby exerting excruciating burden on the limited health resources, especially in developing nations. It also increases the cost of health care and morbidity.

Limitations:
The present study has several limitations like the sample size is small and needs further research. It does not include the clinical definition of VAP. A control group of non-VAP patients was not included to compare the results and determine their significance in terms of p-value. Risk factors underlying the occurrence of VAP were not taken into consideration. The results of the study may not be applicable to other sites.

CONCLUSION:
VAP is a common morbid nosocomial infection in mechanically ventilated patients in ICUs which prolongs the duration of hospital stay and increases the cost of health care. This makes it prudent to study and document the local bacterial pattern prevalent and their antimicrobial sensitivity in order to ensure timely initiation of empirical antibiotic therapy. A local antibiogram with periodic updating will help use antibiotics appropriately and judiciously, thereby curbing down the morbidity and mortality associated with VAP. Proper implementation of infection control measures and aseptic bundles will also help reduce the incidence of VAP in critical care setting. Judicious use of mechanical ventilation along with early weaning off will also help reduce the incidence of VAP. Large multi-center trials are needed to understand the risk factors and their relation in causation of VAP, to ensure appropriate implementation of preventive measures.

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