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RESEARCH ARTICLE

A STUDY ON INCIDENCE, RISK FACTORS AND MICROBIOLOGICAL PROFILE OF VENTILATOR ASSOCIATED PNEUMONIA IN A TERTIARY CARE REFERRAL CENTRE: KERALA, SOUTH INDIA

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is the most common nosocomial infection diagnosed in the intensive care unit (ICU) and in spite of advances in diagnostic techniques and management it remains a common cause of hospital morbidity and mortality.
Aims/objective: The aim of the study was to determine the incidence, the bacterial pathogens causing VAP in our setup, along with the susceptibility pattern for antibiotics and detect the multi-drug resistant pathogens among them.
Materials and Methods: This prospective study was conducted in department of Critical Care Medicine, Lakeshore hospital & research centre over a period of 2 years from November 2014 to October 2016, enrolling patients undergoing mechanical ventilation for >48h in MICU's. Exclusion criteria- age <12 years, patients with COPD, Tuberculosis, ARDS, Bronchial asthma on admission & patients with Pneumonia prior to or within 48 hours of mechanical ventilation are excluded from the study .Endotracheal aspirates were collected from patients with suspected VAP and semi-quantitative cultures were performed on all samples. VAP was diagnosed using Clinical Pulmonary Infection Score (CPIS).
Results: Out of 100 cases studied, 19 (19%) patients were diagnosed to have VAP, out of which 42.11% had early-onset (< 96 hours of mechanical ventilation) VAP and 57.89% had late-onset (>96 hours of mechanical ventilation) VAP. Ventilator associated pneumonia was more preponderant in males (63.15), the commonest age group being >60 years followed by age group 41 to 50 years (26.3%). Reintubation of more than one times, infection at other sites and prolonged ventilation are the risk factors for VAP. Acinetobacter species followed by Pseudomonas aeruginosa were the most commonly isolated pathogens in both types of VAP. Antibiotic sensitivity pattern revealed most of the pathogens to be multi-drug resistant. There is significant difference in VAP and Non-VAP groups in terms of outcome variables like death, and discharge from the hospital. Motality rate in our study was 26%, which was significantly higher in late onset VAP due to MDR pathogens. VAP prolongs the duration of mechanical ventilation, length of intensive care and the duration of hospital stay compared to the Non VAP cases.
Conclusions: This study provides a baseline data of current scenario of VAP in our set up, which can be utilized to formulate infection control strategies. The present study also shows that VAP is increasingly associated with MDR pathogens which lead to increased mortality, morbidity and indirectly the health care costs.

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INTRODUCTION

Ventilator-Associated Pneumonia (VAP): a subgroup of hospital acquired pneumonia, is a highly lethal form contracted by patients on ventilators in hospitals and long-term nursing facilities. Ventilator associated pneumonia (VAP) is defined as pneumonia that occurs 48–72 hours or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent.1

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VAP contributes to approximately half of all cases of hospital-acquired pneumonia. 1 It is the second most common nosocomial infection in the intensive care unit (ICU) and the most common in mechanically ventilated patients. 2,3. VAP is commonly classified as either early onset (occurring within 96 hours of start of mechanical ventilation) or late onset (>96 hours after start of mechanical ventilation),4. It is a common condition, difficult to diagnose accurately and expensive to treat. It development prolongs a patient's stay in the Intensive care unit (ICU), and is associated with significant morbidity and mortality. VAP requires a rapid diagnosis and initiation of the appropriate antibiotic treatment since many studies have shown that delayed administration of appropriate antibiotic therapy in patients with VAP has been associated with increased mortality. 5, 6. VAP is estimated to occur in 9–27 %

of all mechanically ventilated patients, with the highest risk being early in the course of hospitalization.1,3. Risk for VAP is greatest during the first 5 days of mechanical ventilation (3%) with the mean duration between intubation and development of VAP being 3.3 days.1,7 This risk declines to 2%/day between days 5 to 10 of ventilation, and 1%/day thereafter.1,8 Differences in VAP incidences have been based on the antibiotic profile, ICU environment, and the population of study.9. According to The National Nosocomial Infection Surveillance Program the incidence of VAP is 7.6 case per 1000 patient ventilator days.10. This difference is a result of the diversity of diagnostic methods used. Mortality is high when VAP is associated with Multi Drug Resistant (MDR) pathogens like Acinetobacter, Klebsiella, Pseudomonas and E.coli. India has an overall crude mortality of 67.4% in ICU patients with pneumonia, with 40% of the mortality in these patients attributable to infection alone.11, The organisms commonly implicated for VAP are gram positive and gram negative bacteria, 12, of which Klebsiella is most common culprit.13 Early nset VAP (within 5 days of ventilation) results from aspiration of endogenous community acquired organisms e.g. S. pneumoniae, H.influenzae, and aerobic gram negative bacilli. Late onset VAP (5 or more days after initiation of ventilation) results from aspiration of gastric/oropharyngeal secretions and is caused by potentially drug resistant organisms like methicillin resistant Staphylococcus and Pseudomonas. The diagnosis of pneumonia in mechanically ventilated patients is difficult, and there is no "gold-standard" established as a specific diagnostic method. It is usually based on the combination of clinical, radiological and microbiological criteria defined by Clinical Pulmonary Infection Score (CPIS). To the best of our knowledge this study is first of its kind in Kochi-Kerala, South India to know the incidence, risk factors, pathological profile and outcome of ventilator associated pneumonia in our Multidisciplinary Intensive Care Units (MICUs). Such a study is essential to determine the effective strategies for its prevention and formulating an antibiotic policy.

Aims and objectives

The aim of the study was to determine the incidence, identify the probable risk factors, most common bacterial pathogen causing VAP, & to detect the presence of drug resistant pathogens.

MARERIALS AND METHODS

This prospective study was conducted in department of Critical Care Medicine & Anesthesiology, Lakeshore hospital & research centre over a period of 2 years from November 2014 to October 2016, enrolling patients undergoing mechanical ventilation for >48h in MICU's. Exclusion criteria- age <12 years, patients with COPD, Tuberculosis, ARDS, Bronchail asthma on admission & patients with Pneumonia prior to or within 48 hours of mechanical ventilation were excluded from the study. Endotracheal aspirates were collected from patients with suspected VAP and semi-quantitative cultures were performed on all samples. VAP was diagnosed using Clinical Pulmonary Infection Score (CPIS). 100 patients admitted into the Multidisciplinary Intensive Care Unit (MICU) at Lakshore Hospital, who satisfied the inclusion criteria, were enrolled for the study. The study was approved by the institute ethics committee. Informed consent was obtained from the patient's next of kin.

Statistical Methods

Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. Odds ratio has been used to assess the influence of risk factors in relation to the incidence of VAP.

RESULTS

Out of 100 cases studied, 19 (19%) patients were diagnosed to have VAP, out of which 42.11 % had early - onset (< 96 hours of mechanical ventilation) VAP and 57.89% had late-onset (>96 hours of mechanical ventilation) VAP. Ventilator associated pneumonia was more preponderant in males (63.15), the commonest age group being >60 years followed by age group 41 to 50 years (26.3%).

Table 1. Total number of study population (n) = 100

Patients	VAP	Non-VAP	Total
Number	19	81	100

Out of the 100 patients studied, 19 were VAP accounting for 19% of the cases. VAP is considered when the CPIS score is more than 6.

Table 2. Onset of VAP

Onset of VAP	Number of VAP	%
Early onset	8	42.11
Late onset	11	57.89
Total	19	100

Out of 19 diagnosed VAP cases 41.17% of the VAP cases were early onset VAP and the remaining 57.89% were late onset VAP.

Table 3. Gender distribution in VAP patients

GENDER	NUMBER(n=19)	PERCENTAGE
MALE	12	63.15
FEMALE	7	36.85

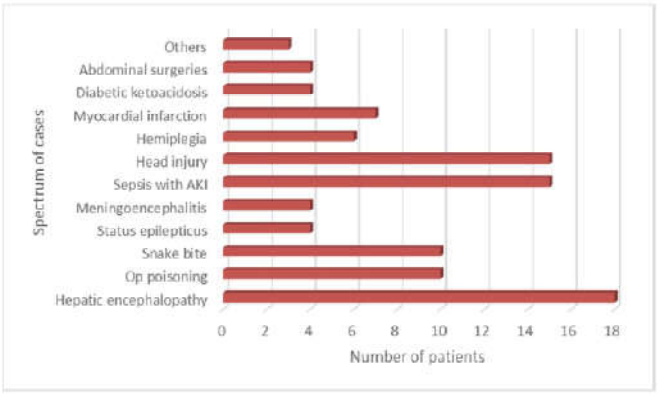
Out of 19 VAP patients, 12 (63.15%) patients were males and 7 (36.85%) were females.

Table 4. Incidence of VAP in different age groups of study population

Age	No of VAP cases	%
21-30	1	5.2
31-40	3	15.8
41-50	5	26.3
51-60	4	21
>60	6	31.6

The most common age group associated with VAP is >60 years (31.6%) followed by age group 41 to 50 years (26.3%). The less affected group is 21-30 years with incidence of 5.2%. The indication for ICU admission requiring ventilator support is given in the above table where hepatic encephalopathy (18%) was the major cause followed by sepsis (15%) and head injury (15%). Other causes include organophosphorus poisoning (10%), snake bite (10%), myocardial infarction etc.

Table 5: Spectrum of cases in the study population



>50% of the patients who had >1 intubations developed VAP, which is statistically significant (p< 0.0001).Higher the number of intubation greater the chances of developing VAP and also there is chance of VAP with 2 or less intubations.

Table 6. Comparison of the number of intubations with VAP and Non-VAP cases

No of intubations	Total	VAP	Non-VAP	P value
1	80	8	72	<0.0001*
>1	20	11	09	

Table 7. Comparison of tracheostomy with VAP and Non-VAP cases

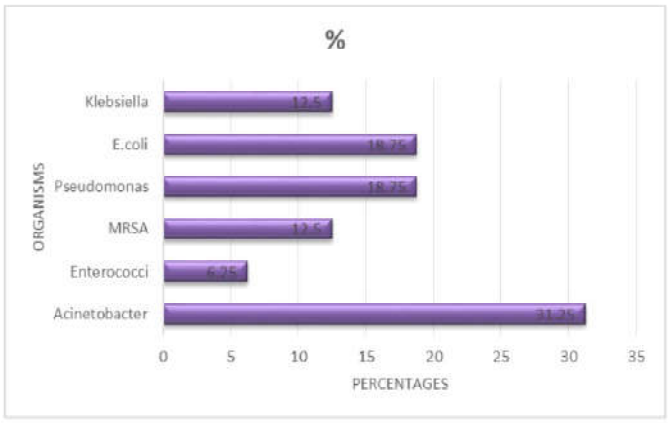
	Total	VAP	Non-VAP	P value
Tracheostomy	22	10	12	0.001*
No tracheostomy	78	9	69	

Out of 22 who undergone tracheostomy 10 developed VAP (45.45%) which is statistically significant (p=0.001). There is no significant difference among early and delayed tracheostomy groups.

Table 8. Comparison of MV duration, ICU stay and Hospital stay in VAP and Non- VAP groups

	VAP	Non-VAP	P value
MV duration	13.3±4.24	4.17±1.97	<0.0001
ICU stay	16.05±5.27	5.81±1.97	<0.0001
Hospital stay	20.15±7.39	7.83±2.38	<0.0001

Table 9. organisms isolated in VAP group



In the study population VAP is associated with prolonged MV duration, ICU stay and Hospital stay which is statistically significant (p <0.0001). Out of 16 isolates from VAP patients major organism isolated was Acinetobacter (31.25%) followed by E.coli and Pseudomonas (18.75%).

Table 10. Endotracheal isolates showing the spectrum of organisms in early and late onset of VAP

Isolate	Total(n=16)	Early onset(n=6)	Late onset(n=10)
Acinetobacter	5	0 (0%)	5(100%)
E.coli	3	1(33.3%)	2(66.7%)
Klebsiella	2	1(50%)	1(50%)
Pseudomonas	3	1(33.3%)	2(66.7%)
MRSA	2	2(100%)	0
Enterococci	1	1(100%)	0
MSSA	0		0

Out of 16 isolates from VAP cases 10 isolates from late onset VAP and all of them were gram negative organisms. Gram positive organisms were found in early onset VAP cases.

Table 11. Resistance pattern in isolated organism

Resistance	Number of organisms
ESBL	5
MRSA	2
MBL	6
Amp C	0

Out of 30 organisms isolated from all ventilated patients 13 isolates found to be high resistant organisms. Among these 13 majority were (46%) metallo betalactamase producing organisms followed by extended spectrum betalactamase producing (39%) organisms. Two MRSA were isolated.

Table 12. Outcome comparison in VAP and Non-VAP groups

Outcome	Total	VAP	Non-VAP	P value
Discharged	80	12	68	.028977
Death	10	5	5	
Discharge against medical advice	10	2	8	

There is significant difference in VAP and Non-VAP groups in terms of outcome variables like death, discharge against medical advice and discharge (p=.028977).

Table 13. Outcome in early and late onset of VAP

Outcome	Total	Early onset	Late onset	P value
Death	5	2	3	.969876
DAMA	2	1	1	
Discharge	12	5	7	

There is no significant difference in early and late onset VAP groups in terms of outcome variables like death, discharge against medical advice and discharge (p=.9698).

DISCUSSION

Ventilator associated pneumonia is an important type of hospital acquired infection. VAP may be caused by a wide spectrum of bacterial pathogens, either polymicrobial or rarely due to viral or fungal pathogens in immunocompetent hosts. Multi-drug resistant pathogens causing VAP are a major concern in any kind of ICU set up. This study was planned to detect the bacterial pathogens causing VAP among patients

who were mechanically ventilated in the Medical Intensive Care Units of our tertiary care referral hospital. In our study the incidence of VAP was found to be 19%, which is similar to several other studies conducted , Table given below shows that the the incidence of VAP reported by recent studies ranging from 17% by Cook DJ *et al* to 45.4 % by Dey *et al*, 14.

Study	Year	Vap rates (%)
Dey *et al* (14)	2007	45.4%
Joseph *et al* (18)	2009	18%
Mukhopadhyayetal (15)	2010	42%
Reena *et al* (26)	2011	27.22%
Amit khelgi (27)	2014	27.5%
Saileela *et al* (16)	2014	33.47%
Current study	2015	19%

Out of the 19 cases of VAP, 42.11% were early-onset and 57.89% were categorized as late-onset. Similar results were obtained by Mukhopadhyay *et al* 15 with 38% being early-onset VAP and 62% late-onset VAP and one another Indian study which was carried out in a tertiary center in Bangalore 2012 by Amit *et al* showed similar results where early onset VAP cases were 42% and late onset were 58%. In one recent study from Hyderabad in 2014 showed 30.86% of early onset of VAP, 69.13% late onset VAP.16 Of the 19 patients who developed VAP 12 (63.15%) were male and 7 (36.85%) were female. In a study conducted by Eleni Apostolopoulou *et al* (17) 71% were male and 29% were female. In a study conducted in India by Joseph *et al* 66.7 % were male and 33.3 % were female.18 In our study VAP was most seen in age group of > 60 years followed by 41- 50 years group. This is different from few other recent studies where majority of VAP cases occurred in 41-60 years age group. A study by Dey *et al*14 showed the most common age group to acquire VAP was between 46-60 years. The mean age for developing VAP was 45 years in study by Mukhopadhyay *et al*. 15

In the present study, 81.25% Gram negative bacilli and 18.75% Gram positive cocci were isolated from specimens collected from VAP cases. Rajesh chawla *et al* 19 in their study also found that 87% of patients with VAP were infected with Gram negative bacilli. Previous studies conducted show that Pseudomonas aeruginosa was the most common Gram negative bacilli causing VAP. 20,21. The present study showed that Acinetobacter spp. was the commonest isolate (37.83%) with Pseudomonas aeruginosa (24.32%), Klebsiella pneumonia (13.52%) and Escherichia coli (10.81%) being the other common isolates from the specimen. Acinetobacter species followed by pseudomonas aeruginosa was found to be the most common organism in both early and late onset VAP. Similar findings were reported by Dey *et al* 14 where Acinetobacter species was the commonest (48.94%) organism causing early and late onset VAP followed by P. aeruginosa (25.53%). Lakeshore Hospital and Reserch Centre is a tertiary care referral center, where most of the patients admitted are referred after being treated in primary care facilities with antibiotics, most commonly third generation cephalosporins and fluoroquinolones. A study conducted by Mulin *et al*, 22 showed the association of third generation cephalosporins with colonization and infection with Acinetobactor baumanni. Previous use of Fluoroquinolones was a risk factor for the development of endemic A. baumannii infection. Acinetobacter species are particularly important in causing outbreaks and readily spread from one patient to another. This appears to be due to their ability to survive on the hands of health care workers and inanimate environmental surfaces and their intrinsic resistance to many common antibiotics rather than any potent virulence factors aimed at host defenses. Previous studies have shown methicillin sensitive Staphylococcus aureus (MSSA) or resistant Staphylococcus aureus (MRSA) to be a major causative agent of early-onset VAP.11, 23. In our study only 2 isolates of MRSA causing early-onset VAP were isolated. This indicates that the causative pathogens may vary in different settings. Although the study population and number of isolates may not be representative of the scenario, further studies are needed to strengthen the outcomes of the present study and help clinicians to initiate early prophylactic treatment in the group of patients on mechanical ventilation and at risk of developing VAP. Multidrug-resistant organisms are on the rise in intensive care settings. Antimicrobial susceptibility pattern of the isolates obtained in the present study showed that most of the Gram negative bacilli were multidrug resistant. Acinetobacter species and P.aeruginosa were found to be resistant to most of the classes of antibiotics in current use including carbapenems. Enterobacteriaceae isolated showed a high level of resistance to beta-lactam antibiotics and were sensitive to carbapenems. Such a high level of drug resistance has also been documented in studies conducted by Joseph *et al* 18 and Dey *et al*.14 Similar kind of resistance pattern seen in recent study done in Hyderabad in 2014.16

Presently there is concern about the acquisition of plasmid-mediated metallobeta- lactamases active against carbapenems and antipseudomonal penicillins and cephalosporins.24 Although Acinetobacter spp are generally less virulent than P.aeruginosa, these have nonetheless become dreaded pathogens because of increasing resistance to commonly used antimicrobial agents.24 More than 85% of isolates generally are susceptible to carbapenems, but resistance is increasing due either to IMP-type metalloenzymes or carbapenemases of the OXA- type. In our study 44.44% (4/9) of Acinetobacter and 33.3 % (1/3) of Pseudomonas spp were plasmid-mediated MBL producing strains. Emergence of Extended spectrum beta lactamases (ESBLs) and AmpC betalactamases in a hospital set up are of increasing concern. ESBLs are most commonly produced by Klebsiella spp and Escherichia coli but may also occur in other Gram negative bacteria. They are typically plasmid mediated; clavulanate susceptible enzymes hydrolyse penicillins, expanded-spectrum cephalosporins and aztreonam. Among the isolates obtained in the present study, 50% (1/2) of K.pneumoniae, 80% (4/5) of Escherichia coli were found to be ESBL producers. The high incidence of ESBL and MBL producing organisms obtained in the study are a major concern which need to be addressed in terms of curbing inadvertent use of antibiotics and designing an effective infection control policy. Although the limitations of the current study remains to be a relatively fewer number of isolates which can be overcome by continuing to monitor this aspect as a part of the quality indicator determining control of hospital acquired infections. In the present study, it was found that the mortality rate among these patients was 26%. Similar findings were reported in studies undertaken by Panwar *et al* 25 where mortality rates were found to be 37% which showed an increase with the duration of mechanical ventilation. In one recent study from Hyderabad showed mortality rate of 16%.16. It was seen that the mortality was significantly high in patients with late-onset VAP caused by multidrug resistant Acinetobacter and Pseudomonas infection. The difference in mortality rates in different institutes is based on study population, difference in antibiotic and ICU protocols.

Disclosure: The authors report no conflicts of interest in this work.

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