

Ventilator-associated pneumonia: A persistent healthcare problem in Indian Intensive Care Units!

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is the most common nosocomial infection acquired by patients in the Intensive Care Unit (ICU). However, there are scarce clinical data, particularly from Indian ICUs on the occurrence of this infection. **Aims:** To collect data on the incidence, microbiological profile, and outcomes of patients with VAP. **Settings and Design:** Tertiary level, medical-surgical ICU; prospective, observational study. **Subjects and Methods:** All patients who were mechanically ventilated for >48 h in the ICU during the study were enrolled. VAP was diagnosed according to the Centre for Disease Control (CDC) criteria. **Results:** A total of 95 (38%) patients developed VAP infections, an incidence of 40.1 VAP infections/1000 mechanical ventilation days. These were predominantly caused by Gram-negative organisms, especially the *Acinetobacter* species (58 isolates, 53.2%). Many of the VAP-causing isolates (27.3%) demonstrated multidrug resistance. Patients with VAP infections experienced a significantly longer ICU stay (13 days [Interquartile Range (IQ) range = 10–21] vs. 6 days [IQ = 4–8], $P < 0.0001$) and total hospital stay (21 days [IQ = 14–33] vs. 11 days [IQ = 6–18], $P < 0.0001$). While the overall mortality rates were similar between patients with or without VAP infections, (68.4% vs. 61.3%, $P = 0.200$), on subgroup analysis, elderly patients (>60 years) and those with higher Acute Physiology and Chronic Health Evaluation II scores at admission had significantly greater mortality rates if they acquired a VAP infection ($P = 0.010$). **Conclusions:** VAP continues to be a major threat to patients who are admitted for mechanical ventilation into the critical care unit, emphasizing the urgent need for infection control measures.

KEY WORDS: Incidence, Intensive Care Unit, microbiological profile, outcome, ventilator-associated pneumonia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is reported to be the most common device-associated nosocomial infection acquired among patients who are mechanically ventilated in the Intensive Care Unit (ICU). While the international nosocomial infection control consortium (INICC) data suggests a VAP incidence as high as 13.6/1000 mechanical ventilation (MV) days.^[1] The occurrence of VAP in Asian countries is much higher, and ranges from 3.5 to 46 infections/1000 MV days.^[2] This prospective audit was

conducted to study the incidence demographic and microbiological characteristics and outcomes of patients developing VAP in a tertiary level ICU in Northern India.

SUBJECTS AND METHODS

This was a prospective observational study, conducted in the adult ICU of a tertiary care hospital in North India from December 1, 2010–November 30, 2011. All patients over 18 years of age, who were intubated

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and mechanically ventilated for more than 48 h, were included in the study. Patients, who were intubated or on mechanical ventilation for more than 12 h before admission to the ICU, were excluded. At enrollment, the following baseline variables were noted: age, gender, date of hospital and ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, the category of admission (trauma, medical, or surgical patients), diagnosis at admission and presence of any comorbid conditions. All study patients were followed up daily and evaluated for the signs and symptoms of VAP infection according to the definition set by Centre for Disease Control (CDC) and Prevention National Healthcare Safety Network (NHSN). Standard ventilator care which includes head end elevation, peptic ulcer prophylaxis, deep vein thrombosis prophylaxis, and daily sedation hold were provided to all patients as a part of the ICU care protocol. A diagnosis of VAP was made in all patients fulfilling the CDC definition of VAP from 48 h following the initiation of mechanical ventilation till 48 h postextubation. On being diagnosed with VAP, the clinical pulmonary infection score was calculated (a score of >6 was considered as highly significant of VAP). Respiratory samples were collected by deep sterile endotracheal suctioning and sent to the laboratory within 1 h for microbiological analysis. Gram-staining and culture were performed on all respiratory samples and antibiotic sensitivity patterns were noted. All included patients were followed up daily to study their clinical progress and outcomes. The duration of mechanical ventilation, the length of ICU stay and hospital stay, as well as the status on discharge, i.e., whether alive or dead were noted.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) The Chi-square test or Fisher’s exact test was used to compare different groups. Univariate analysis was used to compare the variables for the outcome groups of interest (patients with VAP vs. patients without VAP). Comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were compared using Student’s *t*-test for normally distributed variables. We confirmed the results of these tests, with logistic regression analysis, using statistics software (SPSS 16.0, SPSS Inc., Chicago, Illinois, USA). All *P* < 0.05 were considered statistically significant.

RESULTS

During the study, 845 patients were admitted in the ICU, of which 250 patients fulfilled the inclusion criteria [Figure 1]. The majority of patients (149, 59.6%) were males with a mean age of 53.60 (± SD 18.03) years. The average APACHE II score at admission was 20.74 (± SD 6.75) and most patients (192, 76.8%) were admitted under the medical category.

A total of 95 (38%) patients developed VAP during the study, an incidence of 40.1 episodes of infection/1000

mechanical ventilation (MV) days. The device utilization ratio was 0.85. While there was no association of VAP with any of the co-morbid illnesses such as diabetes mellitus and hypertension male patients were found to be at a greater risk for developing VAP infections [Table 1].

Microbiological evaluation was performed on 109 respiratory samples collected from 94 patients suspected to have VAP infection. Gram-negative organisms were isolated in 95 samples, Gram-positive organisms in five samples while nine samples did not show any growth. On culture, the most common organisms grown were *Acinetobacter* (58 isolates, 53.2%), *Klebsiella* (17 isolates, 15.6%), *Pseudomonas* (14 isolates, 12.8%), and *Escherichia coli* (nine isolates, 8.25%). Of the five Gram-positive isolates, one (0.9%) was found to be methicillin-sensitive *Staphylococcus aureus* (MSSA) and 4 (3.6%) were methicillin-resistant *S. aureus* (MRSA). Six (5.5%) samples yielded fungal organisms, which included *Candida albicans* (in one isolate) and *Candida nonalbicans* (in five

Table 1: Univariate analysis of the demographic characteristics between patients with ventilator-associated pneumonia and without ventilator-associated pneumonia

Characteristics	VAP ^a (n=95) (%)	Non-VAP (n=155) (%)	P ^b
Age (years)			
Mean±SD ^c	55.49±17.45	52.43±18.40	0.19
Gender			
Males	65 (68)	84 (54)	0.03
APACHE II			
Mean±SD ^c	21.41±6.73	20.32±6.75	0.21
Type of admission			
Medical/surgical	72/23	120/35	0.18
Co-morbidities			
Diabetes	33 (35)	56 (36)	0.82
Hypertension	50 (53)	71 (46)	0.29
IHD ^d	27 (28)	33 (21)	0.20
Obesity	13 (14)	19 (12)	0.74
COPD ^e	17 (18)	18 (12)	0.16
Smoking	20 (21)	21 (14)	0.12
Alcoholism	22 (23)	27 (17)	0.26
Steroid use	11 (12)	18 (12)	0.99

^aVAP: Ventilator-associated pneumonia, ^b*P*<0.05 was considered significant. ^cSD: Standard deviation, ^dIHD: Ischemic heart disease, ^eCOPD: Chronic obstructive heart disease

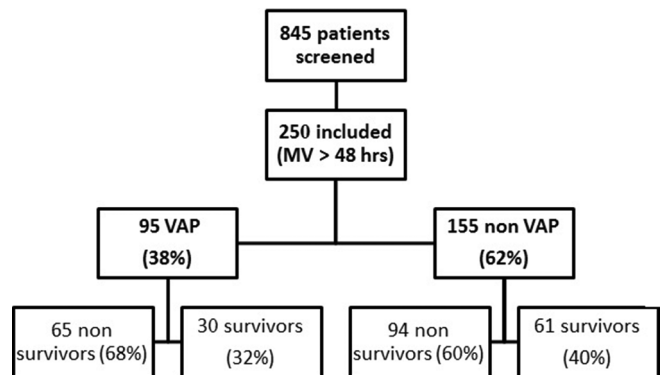


Figure 1: The process of screening, selection and the outcomes of patients studied

isolates) [Figure 2]. Fifteen patients had polymicrobial flora in their tracheobronchial secretions, namely, combinations of Gram-negative organisms, viz., *Acinetobacter*, *Klebsiella* and *Pseudomonas*. Many of the isolated organisms exhibited resistance to the commonly used antibiotics and 26 (27.3%) patients were found to be infected with multidrug-resistant (MDR) organisms. There were a high proportion of Extended Spectrum β Lactamases (ESBL) producing strains among *Klebsiella* species (13 isolates, 76.5%) and *E. coli* (5 isolates, 55.55%) strains. While all strains of *Acinetobacter* were MDR organisms, 25 of these isolates (43.1%) were resistant even to the carbapenem group of antibiotics. A significant number of *Klebsiella* (12 isolates, 70%) and *Pseudomonas* (four isolates, 28.5%) isolates also demonstrated resistance to carbapenems.

Twenty-nine patients (30.85%) had developed early-onset VAP (defined as VAP occurring within 4 days of mechanical ventilation) and 65 (69%) patients developed late onset VAP (defined as VAP developing ≥ 5 days of mechanical ventilation). The former occurred by $3.58 \pm SD 0.501$ MV days as compared to $9.59 \pm SD 4.32$ days for late onset VAP. Although the severity of illness (APACHE II score) was comparatively similar in patients with early and late onset VAP ($P = 0.659$), the duration of ICU stay was significantly more in patients who developed late-onset VAP ($10.82 \pm SD 4.39$ days in early vs. $21.04 \pm SD 13.2$ days in late VAP, $P = 0.030$). In both cases, Gram-negative organisms were the main pathogenic organisms found to be responsible for causing VAP, especially *Acinetobacter* species, and MDR pathogens were found in 28 (73.6%) isolates among patients with late VAP as compared to nine (23.6%) isolates among patients with early VAP infections. However, this was not statistically significant ($P = 0.587$).

The duration of mechanical ventilation, the length of stay (LOS) in the ICU and hospital, were all prolonged in patients who had developed VAP infections [Table 2]. While the overall mortality rates were similar between patients with or without VAP infections, subgroup analysis revealed that death rates following VAP infection were higher in the elderly (age >60 years), ($P = 0.010$), and in those with higher mean APACHE II scores ($P = 0.010$).

DISCUSSION

VAP infection is common in the ICU, affecting 8–20% of all ICU patients and up to 27% of mechanically ventilated patients.^[3] A systematic review of VAP infections among adult patients admitted to ICUs in developing countries revealed that the rates of VAP infections varied from 10 to 41.7/1000 MV-days, and were generally higher than NHSN benchmark rates.^[4] VAP is associated with considerable morbidity, including prolonged ICU LOS, prolonged mechanical ventilation, and increased costs of hospitalization.^[3-6] According to the NHSN report, data

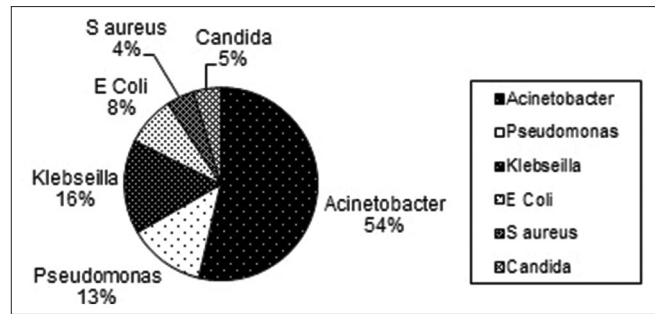


Figure 2: Microbiological organisms isolated in patients with ventilator-associated pneumonia infections (with percentages). Gram-negative organisms caused a large majority of ventilator-associated pneumonia infections with *Acinetobacter* being the single largest species isolated

Table 2: Comparison of the outcome variables between patients with ventilator-associated pneumonia versus nonventilator-associated pneumonia

Variables	Median (IQR)		P ^b
	VAP ^a (n=95)	Non-VAP (n=155)	
APACHE II ^d	22 (15-26)	21 (14-26)	0.26
Total MV ^e days	12 (8-19)	4 (4-7)	<0.0001
LOS ^f			
ICU	13 (10-21)	6 (4-8)	<0.0001
Hospital	21 (14-33)	11 (6-18)	<0.0001
Mortality (%)	65 (68.4)	95 (61.3)	0.200

^aVAP: Ventilator-associated pneumonia, ^b $P < 0.05$ was considered significant. ^cIQ: Interquartile range, ^dAPACHE II score: Acute Physiology and Chronic Health Evaluation II score, ^eLOS: Length of stay, ICU: Intensive Care Unit, eMV: Mechanical Ventilation, fLOS: Length of Stay

summary for 2012, all device-associated infection rates, including VAP rates, are found to be higher in major teaching locations as compared to their counterparts, with burn critical care locations having the highest percentage of the device-associated infections.^[7]

This study revealed high VAP rates among patients who were mechanically ventilated in the ICU, i.e., 37.5% infection, with 40.1 VAP episodes/1000 MV days. The average VAP rates reported by other Indian studies ranged from 8.9 to 46 VAP episodes per 1000 MV days.^[8]

The INICC data, which studied nosocomial infections from eight developing countries over 4 years, stated that VAP infection, with an overall incidence of 41.5%, or 24.1 cases/1000 mechanical ventilation days, posed the greatest challenge for treatment among all the Healthcare-associated infections (HCAIs).^[9] Our study found no significant association between VAP and the demographic factors studied, except for male gender. In previous studies, the risk factors for VAP infections have been found to include, male sex, elderly age, higher APACHE II scores, prolonged antibiotic usage, immunosuppression, reintubation, etc.^[2]

Gram-negative organisms were the predominant pathogens causing VAP infections in our study, a finding similar to other Asian studies.^[2] A recent report presented by

a panel of experts from ten Asian countries suggested that the prevalence of MDR pathogens is rising in Asian countries, and *Acinetobacter baumannii-calcoaceticus* complex is emerging as a major pathogen in most of these ICUs.^[2] Another Indian study reported that most cases of VAP found in their tertiary level ICU were caused by Gram-negative bacteria, (80.9%) such as *Pseudomonas aeruginosa* (21.3%) and *A. baumannii* (21.3%).^[8]

We noted that a high proportion of our VAP infections too, were caused by MDR pathogens, including carbapenem-resistant organisms. This is cause for serious concern. “MDR” pathogens are referred to bacteria such as *Pseudomonas* species, *Acinetobacter* species, MRSA, and enteric Gram-negative bacilli expressing ESBL and AmpC β -lactamases and characteristically, displaying high levels of antibiotic resistance.^[3] The INICC data from eight developing countries reported that Enterobacteriaceae species (26%, with 58% resistant to ceftriaxone) was the most common isolate found to cause VAP infections. This was followed by *P. aeruginosa*, *S. aureus* (77.5% of which were OXA resistant isolates) and *Acinetobacter* species (with 52.4% isolates resistant to carbapenems).^[9] A 9 month prospective study from an Indian tertiary care hospital reported a 45.4% incidence of VAP, which included 48% of MDR *Acinetobacter* infections and 27% of MDR *Pseudomonas* infections.^[10]

Outcomes associations

The mortality rates among patients with VAP infections range from 20% to 76% in various studies,^[11] with higher rates reported among patients with MDR infections. In two different studies, *Pseudomonas* or *Acinetobacter* pneumonia was associated with high mortality rates of 65% and 87% respectively.^[11] Furthermore, MRSA pneumonia was associated with 86% directly attributable mortality to pneumonia, as compared to 12% mortality rates from MSSA pneumonia.

While our data revealed comparable mortality rates between patients with and without VAP infections. However, the duration of mechanical ventilation, length of ICU and hospital stay were all significantly prolonged in patients with VAP infections. This confirms the results of numerous other studies that showed that the development of nosocomial pneumonia leads to a prolonged hospital stay.^[12]

In a retrospective matched cohort study from a large US in-patient database, the occurrence of VAP infections resulted in a significantly prolonged duration of MV (14.3 ± 15.5 days vs. 4.7 ± 7.0 days), ICU LOS (11.7 ± 11.0 days vs. 5.6 ± 6.1 days), and hospital LOS (25.5 ± 22.8 days vs. 14.0 ± 14.6 days).^[6] In our patients, the high incidence of MDR organisms causing VAP infections among our patients probably contributed to the prolonged stay, as these infections took longer to treat and generally

resulted in a stormier course in the ICU. Implied within this is also the significantly high-cost burden imposed by VAP infections. While a precise and universal evaluation of costs associated with VAP is difficult, the overall cost incurred among VAP patients is reported to be greater. A 3 year retrospective case-control study in a Turkish ICU found that costs spent on VAP patients were approximately 5-fold higher than among noninfected patients.^[13]

This study adds important information to the growing problem of healthcare associated infections in the country. The notable strengths of our study were that it was prospectively conducted, from a clinician's viewpoint, with the diagnosis of VAP based on clinical criteria, and supplemented by microbiological results. To date, most Indian studies on VAP infections are from a laboratory-based perspective. The limitations of our study were that respiratory samples were obtained by blind endotracheal aspiration, and quantitative cultures could not be done on tracheobronchial microbiological aspirates, due to limitation of resources. These may have led to an overestimation of the percentage of infection.

This study highlights the need for urgent infection control, planning, as well as multidisciplinary team participation to combat VAP. This includes implementing measures such as education, increased awareness of hand hygiene measures, reduction of the duration of mechanical ventilation and use of VAP bundles, all of which have been proven to reduce the risk of VAP infections.^[14] The INICC data which studied VAP infections from 44 adult ICUs from 14 developing countries, noted that implementation of a multi-dimensional approach which included, bundle of infection control interventions, education outcome surveillance, process surveillance, feedback of VAP rates and performance feedback of infection control practices resulted in a 55.83% decrease in the rate of VAP infection from 22.0 to 17.2/1000 MV days.^[15] More specifically, the data from 21 ICUs across ten Indian cities demonstrated a 38% decrease in the VAP rates, from 17.43/1000 MV days to 10.81/1000 MV days (relative risk 0.62, 95% confidence interval: 0.5–0.78, $P = 0.0001$) during the same study period, and using the same interventional measures.^[16]

CONCLUSION

We conclude that VAP occurs in a considerable proportion of patients in Indian ICU's and is associated with significant morbidity and prolonged hospitalization. We strongly recommend the introduction of appropriate interventional measures to control the development of VAP infections.

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Conflicts of interest

There are no conflicts of interest.

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