Incidence and attributable costs of ventilator-associated pneumonia (VAP) in a tertiary-level intensive care unit (ICU) in northern India

Ashu Sara Mathaia,∗, Atul Phillipsa, Paramdeep Kaurb, Rajesh Isaacb

a Department of Anaesthesiology and Critical Care, Christian Medical College, Ludhiana 141008, Punjab, India
b Department of Community Medicine, Christian Medical College, Ludhiana 141008, Punjab, India

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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, the economic effects of such infections remain unclear particularly in developing countries.

Methods: Patients who were mechanically ventilated for more than 48 h in the ICU were studied for the occurrence of VAP. Total drug costs and hospital costs were noted, and attributable costs were calculated after adjusting for potential confounders.

Results: Ninety-five (38%) patients who were ventilated for more than 48 h developed VAP, which resulted in an incidence of 40.1 VAP infections/1000 mechanical ventilation days. The patients with VAP experienced significantly longer hospital stay [21 (IQ=14–33) days versus 11 (IQ=6–18) days, P<0.0001] and incurred greater hospital costs [USD $6250.92 (IQ=3525.39–9667.57) versus $2598.84 (IQ=1644.33–4477.65), P<0.0001]. Multiple regression analysis revealed that the cost-driving factors in our study population were the occurrence of VAP infections (P<0.0001) and the duration of hospital stay (P<0.0001). The attributable cost of VAP infection was calculated to be USD $5200 (95% CI = 3245–7152).

∗ Corresponding author. Tel.: +91 9888500240/161 2226506; fax: +91 161 5050599.
E-mail addresses: ashusatish.thomas@gmail.com (A.S. Mathai), atulphillips@yahoo.co.in (A. Phillips), kaurparmdeep@yahoo.com (P. Kaur), rajeshisaac@gmail.com (R. Isaac).
Introduction

Ventilator-associated pneumonia (VAP) is the leading cause of nosocomial infection in intensive care unit (ICU) patients. While the international nosocomial infection control consortium (INICC) data suggests that the incidence of VAP is as high as 13.6/1000 mechanical ventilator (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]. In US hospitals, VAP is the second most costly nosocomial infection at $40,144 (95% CI, $36,286—$44,220) [3]. Similarly, in developing countries, the total costs attributed to patients with VAP infections are nearly five-fold higher than those of other patients [4]. Given the paucity of available data from the Asian subcontinent and the potential significance of the economic burden imposed by this common nosocomial infection, we conducted a prospective audit of all VAP infections that were acquired in our ICU. The primary objective of this audit was to study the incidence and the attributable costs of VAP infections. Additionally, we sought to study the microbiological characteristics of these infections and the outcomes of patients who developed VAP infections.

Materials and methods

Setting and subjects

We conducted this prospective observational study in an adult, tertiary-level ICU in northern India over one year (October 1, 2010 to September 30, 2011). Our ICU is a mixed medical-surgical, tertiary level ICU with approximately 900—1000 admissions per year. After receiving approval from the institutional ethics review board, we studied all of the adult patients who were intubated and mechanically ventilated for more than 48h. We excluded patients who were already intubated and those who were on mechanical ventilation for more than 12h prior to ICU admission.

Data collection

After admission into the ICU, we noted the basic demographic details, including age, gender, Acute Physiology and Chronic Health Evaluation (APACHE II) score at admission, category of admission, diagnosis at admission, and the presence of any comorbid illnesses, of all of the included patients. We also noted any histories of addictions, including smoking, alcohol intake, and the use of narcotic or immunosuppressive drugs. All of the included patients were evaluated daily for clinical signs of VAP using the Centers for Disease Control and Prevention (CDC) criteria. The clinical pulmonary infection score (CPIS) was calculated on the day of clinical suspicion of VAP and on the third day after that. CPIS scores ≥6 were considered to be significant. For all patients with suspected VAP, we collected respiratory samples by blind deep endotracheal aspiration and followed the culture results to note the patterns of infection and the resistance characteristics of the isolated organisms.

We also followed up all patients to note their outcomes (i.e., discharge or death) and the total durations of their stays in the ICU and the hospital. The final bills of patients were accessed to study the drug costs and total hospital costs that were incurred.

Terminology

Ventilator-associated pneumonia (VAP) was defined by the novel onset of pneumonia in ventilated patients over the period of 48h from the initiation of mechanical ventilation until 48h after extubation.

Early onset VAP was defined as VAP that developed in ventilated patients within the first four days (<4 days) of mechanical ventilation.

Late onset VAP was defined as VAP that developed in ventilated patients from the fifth day (≥5 days) of mechanical ventilation.

Conversion rates: all costs were calculated in Indian rupees (INR) and were then converted to US dollars (USD) using the mean purchasing power parity value of the Indian rupee for the year 2011 (1 USD $ = 47.9229 INR; Reserve Bank of India exchange rates available from URL: http://www.rbi.org.in/scripts/PublicationsView.aspx?id=14503 were accessed on 30/12/2013) [5].

Calculation of costs per life saved and per life-year saved: The calculations of the costs per life
saved and per life-year saved for VAP are shown in the Appendix. To calculate the per life-year saved, figures for the life expectancy at birth in India (63 years for males, 66 years for females) were obtained from the 2011 World Health Report [6].

Statistical analyses

The statistical measures used included frequencies, descriptive statistics, Mann—Whitney U-tests and multiple linear regression analysis. To normalize the distribution of the total cost, we used the natural log transformation. The VAP estimates (with 95% confidence intervals) according to mechanical ventilation days, total ICU days and total hospital days were calculated via multiple linear regression models after adjustments for age, APACHE II score and the type of admission. We calculated the attributable cost using a multivariable linear regression model. Regression equations were calculated for both patients with and without VAP infections. The regression model for the VAP patients was adjusted for age, APACHE II score, length of stay in the ICU, length of inpatient stay and the duration of mechanical ventilation before VAP developed. The second model for the non-VAP patients was adjusted for age, APACHE II, length of ICU stay and duration of inpatient stay. The results were back transformed by taking the exponent. The attributable cost was calculated by subtracting the costs calculated via these two models. The statistical analyses were performed with SPSS version 21 (IBM Corp.; Armonk, NY).

Results

Demographic characteristics

During the study period, 845 patients were admitted to the ICU, and 250 of these patients met the inclusion criteria (Fig. 1). The majority of the patients (149, 59.6%) were males, and the mean patient age was 53.60 (±SD 18.03) years. The average APACHE II score at admission was 20.74 (±SD 6.75), and the majority of patients (192, 76.8%) were admitted under the medical category.

A total of 95 (38%) patients developed VAP during the study period, which resulted in an incidence of 40.1 episodes of infection/1000 mechanical ventilation (MV) days. The device utilization ratio was 0.85. While there were no associations between VAP and any comorbid illnesses (e.g., such as diabetes mellitus and hypertension), the male patients were found to be at a greater risk for developing VAP infections (Table 1). The majority of VAP episodes (65 patients, 69%) were late infections (i.e., infections acquired after 5 days of ventilation).

Microbiological characteristics and resistance patterns

The majority of the VAP cases (87.15%) were caused by Gram-negative organisms such as Acinetobacter (58 isolates, 53.2%), Klebsiella (15.6%) and Pseudomonas species (12.8%). Cultures yielded gram-positive organisms in only five instances, and these organisms included methicillin-resistant Staphylococcus aureus (MRSA) in four patients (Fig. 2). Ventilator-associated pneumonia was caused by multidrug-resistant (MDR) organisms in 26 (27.3%) patients. There were high proportions of extended spectrum β lactamase (ESBL)-producing strains among the Klebsiella species (13 isolates, 76.5%) and the Escherichia coli (5 isolates, 55.5%) strains. While all strains of Acinetobacter were MDR organisms, 25 of these isolates (43.1%) were resistant to even the carbapenem group of antibiotics. A significant number of Klebsiella (12 isolates, 70%)
Table 1 Univariate analysis of the demographic characteristics between patients with VAP and without VAP.

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

\(a\) VAP — ventilator associated pneumonia.
\(b\) \(P\) value < 0.05 was considered significant.
\(c\) SD — standard deviation.
\(d\) IHD — ischemic heart disease.
\(e\) COPD — chronic obstructive heart disease.

and *Pseudomonas* (4 isolates, 28.5%) isolates also exhibited resistance to carbapenems.

### Outcomes

The crude in-hospital mortality rates were similar between the VAP and non-VAP patients. However, the patients with VAP infections were mechanically ventilated for longer durations and stayed in both the ICU and the hospital for longer durations \(P < 0.0001; \text{Table 2}\).

### Costs incurred

We found that the total costs incurred for treatment and medications were significantly higher among the VAP patients than the patients without VAP \(P < 0.0001; \text{Table 2}\). When we further

Table 2 Univariate analysis of the outcome variables between patients with VAP versus non-VAP.

<table>
<thead>
<tr>
<th>Variables</th>
<th>VAP(a)</th>
<th>non VAP</th>
<th>(P^b) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 95)</td>
<td>(n = 155)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (IQ(c))</td>
<td>Median (IQ(c))</td>
<td></td>
</tr>
<tr>
<td>APACHE II(d)</td>
<td>22 (15–26)</td>
<td>21 (14–26)</td>
<td>0.26</td>
</tr>
<tr>
<td>Total MV(e) days</td>
<td>12 (8–19)</td>
<td>4 (4–7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ICU</td>
<td>13 (10–21)</td>
<td>6 (4–8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hospital LOS(f)</td>
<td>21 (14–33)</td>
<td>11 (6–18)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Costs incurred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (US$)</td>
<td>6250.92 (3525.39–9667.57)</td>
<td>2598.84 (1644.33–4477.65)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Drugs (US$)</td>
<td>2587.49 (1577.18–4257.15)</td>
<td>930.12 (482.27–2023.08)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>65 (68.4%)</td>
<td>95 (61.3%)</td>
<td>0.200</td>
</tr>
</tbody>
</table>

\(a\) VAP — ventilator associated pneumonia.
\(b\) \(P\) value < 0.05 was considered significant (written in bold).
\(c\) IQ — interquartile range.
\(d\) APACHE II — Acute Physiology and Chronic Health Evaluation score.
\(e\) MV — mechanical ventilation.
\(f\) LOS — length of stay.
studied the cost differences between the patients in each group who survived to hospital discharge, we found that the cost difference between the VAP and non-VAP patients persisted. The cost per life saved was calculated to be USD $28,030.62, and the cost per life-year saved was USD $5143.23 (Appendix A).

The multivariate analysis revealed that the VAP patients required 11 additional days on mechanical ventilation ($P<0.0001$), 10 additional days in the ICU ($P<0.0001$) and four additional total hospital days ($P=0.21$) after controlling for age, category of admission, and severity of illness based on the APACHE II scores. The attributable cost of VAP infection was calculated to be USD $5200 (95% CI = 3245–7152; Fig. 3).

Multiple regression analysis revealed that the cost-driving factors in our study population in the ICU were the presence of VAP infection ($P<0.0001$) and the length of hospital stay ($P<0.0001$; Table 3).

**Discussion**

**Endemic proportions**

Ventilator-associated pneumonia (VAP) has significant effects on morbidity, mortality and the costs incurred by patients hospitalized in ICUs [7–9]. According to the National Healthcare Safety Network (NHSN) report data summary for 2012, the rates of all device-associated infections, including VAP, are higher in major teaching locations than in their non-teaching counterparts, and critical burn care locations have the highest rates of device-associated infections [10].

Our study revealed high VAP rates among patients who were mechanically ventilated in the intensive care unit; i.e., the rate of infection was 37.5%, and there were 40.1 VAP episodes/1000 MV days. The average VAP rates reported in other Indian studies range from 8.9 to 46 VAP episodes per 1000 MV days [11]. The INICC data from studies of

<table>
<thead>
<tr>
<th>Variables</th>
<th>$B$ (95% CI)</th>
<th>Exponentiated $B$ (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.002 (−0.002 to 0.006)</td>
<td>1.002 (0.998–1.006)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total days</td>
<td>0.006 (−0.011 to 0.024)</td>
<td>1.006 (0.989–1.024)</td>
<td>0.49</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>0.013 (−0.004 to 0.029)</td>
<td>1.013 (0.996–1.029)</td>
<td>0.14</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>0.02 (0.015–0.025)</td>
<td>1.020 (1.015–1.025)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.006 (−0.005 to 0.016)</td>
<td>1.006 (0.995–1.016)</td>
<td>0.30</td>
</tr>
<tr>
<td>VAP</td>
<td>0.338 (0.162–0.513)</td>
<td>1.402 (1.175–1.670)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(a\) Regression coefficient.  
\(b\) Confidence interval.  
\(c\) $P$ value $<0.05$ was considered significant (written in bold).
nosocomial infections in eight developing countries over 4 years, revealed that VAP infections, with an overall incidence of 41.5% or 24.1 cases/1000 mechanical ventilation days, pose the greatest challenge for treatment among all HCAIs [12]. Our study found no significant associations between VAP and any of the demographic factors that were studied with the exception of male gender. In previous studies, the reported risk factors for VAP infections have included, male sex, elderly age, higher APACHE II scores, prolonged antibiotic usage, immunosuppression, reintubation, etc. [2].

Microbiological spectrum

Gram-negative pathogens were the predominant cause of VAP infections in our study, and this finding is similar to those of other Asian studies [2,11,12]. A recent report presented by a panel of experts from 10 Asian countries suggested that the prevalence of multirdrug-resistant pathogens is rising in Asian countries and that the Acinetobacter baumannii—calcoaceticus complex is emerging as a major pathogen in the majority of these ICUs [2].

Another Indian study reported that the majority of VAP cases in tertiary-level ICUs are caused by Gram-negative bacteria (80.9%) such as Pseudomonas aeruginosa (21.3%) and Acinetobacter baumannii (21.3%) [11].

We also noted that a high proportion of our VAP infections were caused by MDR pathogens, including carbapenem-resistant, Gram-negative organisms, which is cause for serious concern. “Multidrug-resistant” (MDR) refers to bacterial pathogens, such as Pseudomonas species, Acinetobacter species, MRSA, and enteric Gram-negative bacilli, that express ESBL and AmpC β-lactamases and characteristically exhibit high levels of antibiotic resistance [13,14]. The INICC data from eight developing countries reported that Enterobacteriaceae species (26%, with 58% resistant to ceftriaxone) was the most commonly identified isolate among VAP infections followed by P. aeruginosa, S. aureus (77.5% of which were OXA-resistant isolates) and Acinetobacter species (with 52.4% of the isolates resistant to carbapenems) [12]. A nine-month prospective study from an Indian tertiary care hospital reported a 45.4% incidence of VAP that included MDR Acinetobacter infections (48%) and MDR Pseudomonas infections (27%) [15].

Effects on outcomes

The mortality rates were comparable between the VAP and non-VAP patients in our center. However, other studies have reported significantly higher mortality rates among patients who develop VAP infections [3]. The crude mortality rate in our hospital was higher than that reported in some Indian studies (16–37%) [9,16], while the INICC data for developing countries reported a crude mortality rates of 44.9% among patients who developed VAP [12].

Among the patients who developed VAP infections, the length of stay in the ICU was nearly three-fold greater, and the total hospital stay was double the duration of the patients who did not develop VAP infections. These findings confirm the results of numerous other studies that have shown that the development of nosocomial pneumonia leads to prolonged hospital stays [17–20]. Among our patients, the high incidence of MDR organisms that caused VAP infections probably contributed to the prolonged stays because these infections took longer to treat and generally resulted in poorer courses in the ICU.

Economic effect

In our study, the attributable cost of VAP infection, after adjusting for the variables of age, APACHE II score, length of ICU stay, length of inpatient stay and the duration of mechanical ventilation prior to the development of VAP, was INR rupees 249,199 (95% CI: 155,510—342,745) or USD $5200 (95% CI = 3245—7152). This cost was the result of significantly higher total medication costs, higher drug costs, and increases in the length of ICU stays. Comparisons across studies of the economics of VAP infections are difficult because various studies have used different cost calculation methods. Although the actual cost numbers vary widely, increases in hospital costs that are attributable to VAP infections have been nearly unanimously reported in the relevant studies [21–26]. Although no comparative data from India are available, a Turkish study reported that the daily costs of patients with VAP infections are three-fold greater than those of their counterparts without VAP and that the mean ICU stay length is approximately four-fold longer [22]. In a large matched cohort study of 88,689 patients, the VAP patients were found to a higher overall length of stay (21.8 versus 10.3 days) and a higher mean hospitalization cost ($99,598 versus $59,770) compared to patients who did not develop VAP infections [25]. A systematic review of the clinical and economic consequences of VAP infections revealed that between 10% and 20% of patients who receiving more than 48 h of mechanical ventilation develop VAP infections, and these patients have significantly longer ICU stay lengths and while incurring more than USD $10,019 in additional hospital
Incidence and attributable costs of ventilator-associated pneumonia (VAP)

Costs [26]. Our study also showed that, in addition to VAP, the length of hospital stay was the primary cost-driving factor among ICU patients. Several other studies have also confirmed this finding [27–29].

**Strengths and limitations**

This study is the first hospital-based cost analysis of VAP infections from India and might reflect the effects of the costs of VAP infections in similar resource-poor countries. Due to the significant expenses incurred by this common nosocomial infection among critically ill patients, a cost analysis such as this one is called for. This study might have value for individual institutions that are concerned with the escalating costs of healthcare-associated infections and are charged with the responsibility of reducing healthcare costs. Cost analyses of this type provide valuable information about the economic burden of this disease and enable the study of the efficacy of infection control measures. The other notable strengths of our study were that it was prospectively conducted from the clinician’s perspective, and the diagnoses of VAP were based on clinical criteria and supplemented with microbiological results. The limitations of our study were that the respiratory samples were obtained by blind endotracheal aspiration, and quantitative cultures could not be performed on the aspirates due to resource limitations. These limitations might have led to an over estimation of the incidence of infection.

Our study highlights the need for urgent infection control and planning and the need for multidisciplinary team participation to combat VAP that includes the implementation of measures such as education, increased awareness of hand hygiene measures, reductions in the durations of mechanical ventilation and the use of VAP bundles. All of these measures have been proven to reduce the risk of VAP infection [30,31]. The INICC data regarding VAP infections in 44 adult intensive care units from 14 developing countries revealed that the implementation of a multidimensional approach that includes set infection control interventions, education outcome surveillance, process surveillance, feedback regarding ventilator-associated pneumonia rates and performance feedback regarding infection-control practices resulted in a 55.83% decrease in the rate of ventilator-associated pneumonia from 22.0 per 1000 mechanical ventilator days to 17.2 per 1000 mechanical ventilator days [32]. More specifically, data from 21 ICUs across 10 Indian cities revealed a 38% decrease in the VAP rates from 17.43/1000 mechanical ventilator days to 10.81/1000 mechanical ventilator days (relative risk 0.62, 95% confidence interval 0.5–0.78, P = 0.0001) during the same study period based on the same interventional measures [33].

**Conclusion**

We conclude that VAP occurs in a considerable proportion of patients who undergo mechanical ventilation and is associated with excess costs, substantial morbidity and prolonged hospitalization. Considering the economic effects of VAP and the effects of VAP on the health-care system, we strongly recommend the introduction of appropriate interventional measures prevent the development of VAP.

**Conflict of interest**

None declared.

**Funding**

No funding sources.

**Ethical approval**

Ethical Approval was granted by the Institutional Research and Ethics Committee at Christian Medical College, Ludhiana.

**Appendix A.**

(1) Calculation of the cost per life saved: There were 30 survivors of ventilator-associated pneumonia (VAP) in the ICU during the study period.

Total cost incurred by all VAP patients = USD $840,918.56

Cost per life saved = 840,918.56/30 = USD $28,030.62

(2) Calculation of the cost per life-year saved:

Male deaths from VAP: n = 44, mean age 58.39 years.

Mean life expectancy = 63 years (The World Health Report 2011) [14].

Life-years expected = 63 × 44 = 2772.

Life-years lived = 58.39 × 44 = 2569.

Life-year lost = 2772–2569 = 203.
Female deaths from VAP: \( n = 21 \), mean age = 58.81 years.

Mean life expectancy = 66 years (The World Health Report 2011) [14].

Life-year expected = \( 66 \times 21 = 1386 \).
Life-years lived = 58.81 \( \times 21 = 1235 \).
Life-years lost = 1386 – 1235 = 151.

Total life-years lost = 203 + 151 = 354.
Mean life-years lost for all patients who died from VAP in the ICU = 554/65 = 5.45 years.

Cost per life-year of VAP infection = USD \$28,030.63/5.45 = \$5143.23.

References


Available online at www.sciencedirect.com