Original Article

Ventilator-associated nosocomial pneumonia in intensive care units in Malaysia

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Abstract

Background: The outcome indicator of nosocomial infection (NI) in the intensive care unit (ICU) is used to benchmark the quality of patient care in Malaysia. We conducted a three-year prospective study on the incidences of ventilator-associated pneumonia (VAP), risk factors, and patterns of the microorganisms isolated in three ICUs.

Methodology: A follow-up in prospective cohort surveillance was conducted on patients admitted to an adult medical-surgical ICU of a university hospital and two governmental hospitals in Malaysia from October 2003 to December 2006. VAP was detected using CDC criteria which included clinical manifestation and confirmed endotracheal secretion culture results.

Results: In total, 215 patients (2,306 patient-days) were enrolled into the study. The incidence of ICU-acquired device-related NI was 29.3 % (n = 63). The device-related VAP infection rate was 27.0 % (n = 58), with a mechanical ventilator utilization rate of 88.7%. The death rate due to all ICU-acquired NI including sepsis was 6.5%. The most common causative pathogen was *Klebsiella pneumoniae* (n = 27). Multivariate analysis using Cox regression showed that the risk factors identified were aspiration pneumonia (*HR* = 4.09; 95% *CI* = 1.24, 13.51; *P* = 0.021), cancer (*HR* = 2.51; 95% *CI* = 1.27, 4.97; *P* = 0.008), leucocytosis (*HR*=3.43; 95% *CI*= 1.60, 7.37; *P*=0.002) and duration of mechanical ventilation (*HR*=1.04; 95% *CI* = 1.00, 1.08; *P* = 0.030). Age, gender and race were not identified as risk factors in the multivariable analysis performed.

Conclusion: The incidence of VAP was comparable to that found in the National Nosocomial Infection Surveillance (NNIS) System report of June 1998. The incidence of VAP was considered high for the three hospitals studied.

Key Words: ventilator-associated pneumonia; risk factors; survival analysis, nosocomial infection; intensive care unit, nursing

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Introduction

Ventilator-associated pneumonia (VAP) is associated with significant morbidity and mortality in the intensive care units (ICU) in Western and Asian countries, including Malaysia [1-8]. The incidence of VAP varies from 9% to 27% [8]. The mortality rate varies between 30% and 70% [8]. Therefore, surveillance of VAP received a high level of attention. The outcome indicators of VAP can be used in benchmarking the quality of patient care in Malaysia. Since 2000, the Malaysian surveillance has targeted three site-specific, device-associated infections, including ventilator-associated pneumonia (VAP), central-line-related bloodstream infection (CR-BSI), and catheter-related urinary tract infection (CR-UTI) [4-5]. VAP was noted as the most common nosocomial infection and represents a major threat to all hospitalized patients. Therefore, a study was conducted to examine the incidence and risk factors for device-associated VAP and associated bacterial patterns. In this study, VAP is nosocomial pneumonia among patients on mechanical ventilatory support (by endotracheal tube or tracheostomy) for greater than 48 hours. The VAP rate is defined as the number of ventilator-associated nosocomial pneumonias per 1,000 ventilator-days. Early onset of VAP is defined

as five days and less. The surveillance definition of VAP itself is based on the combination of new radiographic densities, supportive clinical signs, and positive cultures.

Materials and Methods

The aim of the study was to determine the incidence and predictors of VAP over time during intensive care unit (ICU) stay in the three hospitals studied.

Study Design

A continuous prospective cohort study was conducted using a validated surveillance form in an adult medical-surgical ICU of a university hospital and two governmental hospitals in Malaysia from October 2003 to December 2006 following a baseline assessment [5].

Subject and sample size

The study reviewed 864 patients and included 215 patients without infection upon admission into the ICU. Patients with nosocomial infection (NI) upon admission were excluded from the study. Patients who developed NI within 48 hours of admission into ICU were also excluded from the study. The development of new cases of VAP was studied during ICU stay. The 215 patients had endotracheal tubes and were on nursed on a mechanical ventilation system. They also had intravascular devices and indwelling urinary catheters on admission into ICU.

Setting

The hospitals studied were Hospital Universiti Sains Malaysia, Hospital Ipoh, and Hospital Terengganu.

Criteria for Diagnosis

Ventilator-associated pneumonia was diagnosed based on the criteria derived from the Center for Disease Control and Prevention protocol [9]. Diagnosis was further confirmed by positive microbial cultures of tracheal aspirate, full blood counts, blood cultures, radiological findings in chest X-ray and clinical manifestations.

Instrument and Validation

A developed and verified NI surveillance form was used to collect the data [5]. This instrument was used to measure the incidence and risk factors of VAP. The form addressed demographic data; diagnosis on admission, history of illness; severity of illness, nutritional status, medications, antibiotics, laboratory blood results, coagulation profile, liver function tests; clinical evidence of infections; and results of microbiology, laboratory investigations and X-ray findings. The severity of illness was measured with the APACHE III Score (Acute Physiology and Chronic Health Evaluation). The age, gender, cause of admission, severity of underlying diseases and organ dysfunction on admission was assessed by APACHE III. The intensity of treatment was recorded by the TISS. The physiological condition was assessed by SAPS II.

Procedure

The occurrence of ventilator-associated pneumonia (VAP) and risk factors were monitored daily using the surveillance form from case notes, laboratory results, clinical findings and direct observation of researchers during the patients' stay in the ICU. Data was collected from admission until the first diagnosis of VAP. Those patients who were censored were monitored daily until discharged from the ICU and were followed up in the ward for 48 hours. This was to capture VAP which might be manifested in the ward.

Ethical Approval

The Human Ethics and Research Committee, Universiti Sains Malaysia, approved the study in October, 2003. Permission was also obtained from the administration of the three hospitals. Informed consent was requested from the patients' close relatives (husband, wife, children or parents).

Statistical analysis

Data entry and analysis were done using SPSS for Windows Version 12.0.1 [10]. Means and standard deviations (SD) were calculated as required for numerical variables. Frequency and percentages were calculated for categorical variables. NI incidence-density rate was calculated as the number of NI cases per 1,000 patient-days. Ventilator-associated pneumonia rate was calculated as the number of ventilator-associated pneumonia cases per 1,000 "patients on ventilator-days". The Device Utilization Rate (DUR) is the proportion of patient days for which a certain device is used. DUR reflects the number of devices used and is a reflection of the severity of the patient's illness. DUR was calculated as the number of device days per 100 patient-days. Simple Cox Regression and Multivariable Cox Proportional Hazard Model analyses were used to

detect the risk factors for development of VAP over duration of stay in the ICU. The predictors identified were presented with their hazard ratios (exponential coefficient), 95% *CI* Wald statistics, and *P* values.

Results

Characteristics of Subjects

Patients with no signs of infection within 48 hours upon admission were studied. The mean (SD) age of patients was 42 (17.05) years. In total, 215 patients were studied, of whom 72.6% were male and 27.4% were female. More than half of the study population consisted of patients of Malay descent (57.2%), followed by Chinese (19.5%), Indian (19.1%) and other races (4.2%). The mean (SD) of severity scores on admission were Simplified Acute Physiology Score II (SAPS II) score of 45.5 (16.87); Therapeutic Intervention Score System (TISS) score of 50.1 (11.62) and APACHE III score of 87.7 (30.15). The majority of the patients were unconscious with a Glasgow Coma Scale (GCS) score of equal to or less than 8 (54%; *n* = 116), whereas others had GCS score variations between 9 and 14 (17.2%; *n* = 37) and above 14 (28.8%; *n* = 62).

Ventilator-associated pneumonia (VAP)

The VAP incidence rate was 26.5% in the three hospitals within a mean (SD) ICU stay of 12.0 (6.7) days; mean (SD) durations of ventilator utilization were 9.0 (6.0) days and a mean (SD) observation period of 12.0 (5.83) days. The mean (SD) duration for occurrence of the first VAP infection episode was 10.0 (4.9). The crude death rate related to all ICU-acquired device-related NIs in ICU was 6.5%. The total number of patient days in ICU was 2,309; the device-utilization days/1,000 patient days were 2,045 days, and the device-utilization rate was 88.7%.

Microbial Patterns

The most common organisms cultured from tracheal aspirates were *Klebsiella pneumoniae* (*n* = 27), *Acinetobacter species* (*n* = 16), *Pseudomonas aeruginosa* (*n* = 13), *Acinetobacter baumanni (n = 12),* Extended-spectrum beta-lactamase (*ESBL*)-producing *K. pneumoniae* (*n* = 6), *Methicillin resistant Staphylococcus aureus (MRSA)(n = 7), Pseudomonas* species (n = 3); *Staphylococcus aureus (n = 2),* and *Staphylococcus epidermis (n = 2*). VAP were clinically diagnosed based on progressive infiltrate in chest X-rays, leucocytosis, pyrexia above 38.5^{o}C, purulent secretions, and crepitations in lungs, which was in accordance to the CDC criteria for diagnosis of ventilator-associated pneumonia (VAP) [6]. This microbial pattern occurred within a mean average ICU stay of 13.4 (*SD* = 6.14) days. Majority of these organisms were implicated to late onset VAP.

Risk Factors

There were five predictors for VAP in the three ICUs studied. These were aspiration pneumonia, cancer, leucocytosis and duration of mechanical ventilation. Length of stay in ICU, heavy sedation (sedatives and painkillers), duration of usage of endotracheal tube, severity of illness, nutritional status, cerebral haemorrhage, respiratory distress, race, gender, and age were not predictors in the multivariable Cox Proportional Hazard Model analysis. The potential risk factors with crude hazard ratio for nosocomial pneumonia (VAP) are shown in Table 1, and the risk factors with adjusted hazard ratio are shown in Table 2. It was found that shorter usage of mechanical ventilation reduced the risk of developing VAP. Every one-day increase in the usage of mechanical ventilation increased the risk of VAP by 4% (*HR* = 1.04; 95% *CI* = 1.00, 1.08; *P* = 0.030). It was noted that patients with aspiration pneumonia were four times at risk of getting VAP *HR* = 4.09; 95% *CI* = 1.24, 13.51; *P* = 0.021) with poor survival in comparison to patients without aspiration pneumonia. Cancer patients were three times at risk of getting VAP (*HR* = 2.51; 95% *CI* = 1.27, 4.97; *P* = 0.008) in comparison to non-cancer patients.

Therefore, it was concluded that the patients have a high chance of getting VAP with exposure to the mentioned combination of factors in the three hospitals studied. It was observed that the patients who had leucocytosis (25% increased white cell count from baseline) on day five of stay in ICU developed VAP. Leucocytosis was a response to the inflammatory process but was not considered as a risk factor in most literatures. Results in this study suggest that it is possible to use leucocytosis as an indicator for the potential occurrence of VAP (*HR* = 3.43; 95% *CI* = 1.60, 7.37; *P* = 0.002). Age, gender, race, and nutritional status were not identified as risk factors in this study using the Simple Cox Regression and Multivariable Cox Proportional Hazard Model. However, when all covariates were adjusted, the impact of the other prevention protocols studied was not statistically significant in the three ICUs.

Table 1. Potential predictors of ventilator-associated pneumonia (VAP) in ICU using Simple Cox Regression (*n*=215).

Variables (n = 215)	**Crude HR (95% CI)**	**Wald (df)**	**P value**
Heavily sedated	2.04 (1.20; 3.49)	6.84 (1)	0.009
Aspiration Pneumonia	5.20 (1.59; 17.00)	7.44 (1)	0.006
Cancer	2.11 (1.09; 4.10)	4.86 (1)	0.012
General Surgery (GIT)	2.13 (1.23; 3.71)	7.19 (1)	0.007
Leucocytosis	3.90 (1.84; 8.27)	12.62 (1)	0.001
Steroid	2.46 (1.13; 5.36)	5.14 (1)	0.023
Clinical diagnosis of sepsis	4.09 (2.37; 7.06)	25.61 (1)	0.001
Platelet Count			
Normal	1.00	-	-
Abnormal	4.02 (2.22; 7.28)	21.14 (1)	0.001
Coagulation Profile			
Normal	1.00	-	-
Abnormal	3.94 (2.16; 7.21)	19.83 (1)	0.001
APACHE III	1.01 (1.00; 1.02)	3.15 (1)	0.076
Duration of ventilation (days)	1.06 (1.02; 1.09)	11.07 (1)	0.001
Haematocrit	1.06	5.27 (1)	0.022
Admission	(0.96; 1.00)		
Total number of antibiotics	1.23 (1.10; 1.39)	5.58 (1)	0.018
Duration of antibiotics (days)	1.04 (1.01; 1.07)	5.58 (1)	0.018
White cell count (5^{th} day)	1.05 (1.00; 1.09)	4.47 (1)	0.035

Key*:* b = estimated coefficient*; CI* = Confidence Interval*; df* = degrees of freedom*; HR* = hazard ratio; [a]numerical variable; [b]categorical; Coding*:*
No = *0* (reference); Yes = *1;*
Normal = 1 (reference); Abnormal = 2; APACHE III = Acute Physiology and Chronic Health Evaluation

Discussion

Device-related VAP rates in this current study were within 30% to 70%, which is comparably low compared to the studies done by Schurink [8] and Valles [18]. The mean (SD) length of usage of endotracheal tubes with a mechanical ventilation system (mean = 9.5 days; SD = 6.09 days; total patient days = 1,939) is considered low in comparison with the National Nosocomial Infectious Surveillance Report in 2004 [6-7]. The lower rate of nosocomial pneumonia (VAP) in our study in

Table 2. Predictors of VAP using Multivariable Cox Proportional Hazard Model.

Variables (n = 215)	**Adjusted Hazard Ratio (95% *CI*)**	**Wald (*df*)**	***P* value**
[b]Aspiration Pneumonia	4.09 (1.24;13.51)	5.32 (1)	0.021
[b]Cancer	2.51 (1.27; 4.97)	7.01 (1)	0.008
[b]Leucocytosis	3.43 (1.60; 7.37)	10.03 (1)	0.002
[a]Duration of mechanical ventilation	1.04 (1.00; 1.08)	4.71 (1)	0.030

Key: *CI* = Confidence Interval; *df* = degrees of freedom; B = estimated coefficient; [a] numerical variable; [b] categorical Coding: No = 0 (reference); Yes = 1

comparison to other studies [6-8,12-13] could be due to the younger age population, who were well nourished, with a shorter stay in ICU (mean stay in days = 11; SD = 6.52; median = 9.0 days; range = 43), together with a combination of other factors. The other reason could be that different ICUs have different characteristics and risk factors with different pathogenesis [3].

The possible sources of the organisms identified in this study could be due to microaspiration, contaminated suction catheter tip, contaminated water for humidification, non-humidification of air via ventilator system, back flow of contaminated fluid collection in the external mechanical ventilator tubing into the lungs, instillation of distilled fluid or normal saline to dilute the thick tracheal secretion during bronchial toilet, as well as transmission into alveoli via the blood-stream. These organisms identified were again similar to those previously reported [12,16].

The extrinsic risk factors related to medical devices potentially could increase significantly, if the ICUs have a lower nurse-to-patient ratio, and/or are staffed mainly by inexperienced nurses with no post basic qualifications. In the year 2006, Hospital Ipoh and Hospital Universiti Sains Malaysia had many new graduates [14]. The ratio of staff to patient at that period was one staff to three patients or one staff to two patients during evening shifts, night duties, and public holidays. A knowledge, attitude and practice (KAP) study [14] revealed 78 new graduates. The possible reasons for cross-infection could be a break in aseptic practices in the usage of mechanical-ventilation devices, suctioning procedure and non-adherence to principles of hand washing and misuse of gloves during emergencies by the new graduates.

Frequent auscultation of lungs and vigorous suctioning of oro-pharyngeal secretions should be reinforced. Asepsis and frequent hand washing were reinforced during suctioning procedures and management of patients on ventilators. In spite of this, VAP is still high.

Furthermore, it was noted during the course of this study that length of stay can be a potential cause of VAP as well as the outcome of VAP. This was taken into consideration during the collection of data and analysis. Similar statements have been made by other researchers [15].

The potential intrinsic risk factors of nosocomial pneumonia could be severity of illness and heavy sedation. The heavily sedated patients in this study were in a supine position with chest, neck and head elevated. Therefore, heavy sedation was not found as a risk factor in this study. Patients were also weaned off sedation as early as the third day.

A study done by Langer *et al.* [16] suggested a relationship between the causative organisms for VAP and the time it occurred [16]. The causative organisms for VAP which occurred within the first four days of mechanical ventilation (early onset of VAP) were *S. aureus, Streptococcus pneumoniae* and *Haemophilus influenzae*, whereas, Gram-negative organisms were found in 66% of patients with late onset of VAP [16-17]. Since the majority of the cultures in this study was Gram-negative organisms, which occurred in patients after five days of stay in ICU, it can be concluded that the majority of the

patients in these three hospitals had late onset of VAP. A study by Fabregas and Torres [17] suggested that patients' chances of getting VAP increased by 2% per day of mechanical ventilation, but our study showed that Malaysian patients had a 4% greater chance of getting VAP per one day increase in mechanical ventilation.

Future Directions

More Malaysian studies need to be done to compare the occurrence of VAP between patients with acute respiratory distress syndrome (ARDS) and non-ARDS. A study comparing community-acquired pneumonia (CAP) in comparison with ICU-acquired VAP also should be conducted. In the current study, cultures of gastric colonization were not done and compared with tracheal colonization in relation to the risk of VAP. This is another aspect that can be reviewed in future studies. In our study, Gram-negative bacilli and *P. aeruginosa* were found in head injured patients who were on prolonged ventilation. Leakage of colonized sub-glottic secretions around the cuff of the endotracheal tube is an important risk factor for VAP. The effect of dental hygiene, *i.e.*, maintaining healthy gums, vigorous brushing and flossing, as well as frequent oro-pharyngeal suctioning on ICU patients, could reduce VAP. This was not specifically studied in Malaysia. The limitations noted here give direction for future studies.

Conclusion

Further studies in all government and private hospitals in Malaysia need to be done to verify these results. The association of dental hygiene, nursing measures, and medical interventions in relation to reduction of VAP need to be explored in future studies. The results of this study suggest that ensuring the patient's head, neck and chest are elevated at 30 degrees and maintaining oral care alone cannot prevent or reduce VAP.

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