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Original Article

Modifiable risk factors of ventilator-associated pneumonia in non-intensive care unit versus intensive care unit

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Abstract

Introduction: Ventilator-associated pneumonia patients are treated in non-intensive care units because of a shortage of intensive care unit beds in Thailand. Our objective was to assess whether the type of unit and medications prescribed to the patient were associated with ventilator-associated pneumonia and multidrug resistant ventilator-associated pneumonia.

Methodology: A matched case-control study nested in a prospective cohort of mechanical ventilation adult patients in a medical-surgical intensive care unit and five non-intensive care units from March 1 through October 31, 2013. The controls were randomly selected 1:1 with cases and matched based on duration and start date of mechanical ventilation.

Results: 248 ventilator-associated pneumonia and control patients were analyzed. The most common bacteria were multidrug resistant *Acinetobacter baumannii* (82.4%). Compared with patients in the intensive care unit, those in the neurosurgical/surgical non-intensive care units were at higher risk ($p = 0.278$). Proton pump inhibitor was a risk factor ($p = 0.011$), but antibiotic was a protective factor ($p = 0.054$). Broad spectrum antibiotic was a risk factor ($p < 0.001$) for multidrug resistant ventilator-associated pneumonia.

Conclusions: Post-surgical and neurosurgical patients treated in non-intensive care unit settings were at the highest risk of ventilator-associated pneumonia. Our findings suggest that alternative using proton pump inhibitors should be considered based on the risk-benefit of using this medication. In addition, careful stewardship of antibiotic use should be warranted to prevent multidrug resistant ventilator-associated pneumonia.

Key words: Ventilator-associated pneumonia; case-control studies; intensive care units; risk factor.

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Introduction

Ventilator-associated pneumonia (VAP) is the most commonly occurring hospital acquired infection in adult intensive care units (ICUs), especially in Southeast Asia [1]. They are expected to continue to occur in the coming decade [2]. Of the five upper-middle income countries in Asia, Thailand has the second highest VAP rate (8.8 per 1,000 ventilator days) [3]. 74% of VAP patients in Thailand are treated in non-intensive care units (non-ICUs) due to a shortage of ICU beds [4]. A retrospective cohort study in a Thai medical-surgical ICU found the incidence of multidrug resistant *Acinetobacter baumannii* (multidrug resistant -MDR- *A. baumannii*) VAP was 90.2% [5].

Better understanding of the medications taken by patients on mechanical ventilation (MV) can lead to improvement in prevention strategies for VAP and MDR VAP [6]. The importance of antibiotics (particularly broad-spectrum antibiotics), proton pump inhibitors (PPIs), nebulized treatments, sedatives, and steroids [7,8] in the development of VAP is controversial. To our knowledge, no previously published study assessed the role of these medications in hospitals where mechanical ventilation occurs more commonly in non-ICU compared to ICU settings. This study assessed the association between 1. type of unit where a patient received medical care (non-ICUs and ICU), modifiable medication exposures, and VAP; and 2. type of unit where a patient received medical care (non-ICUs and ICU), modifiable medication exposures, and MDR VAP among patients who developed VAP.

Methodology

Study design and setting

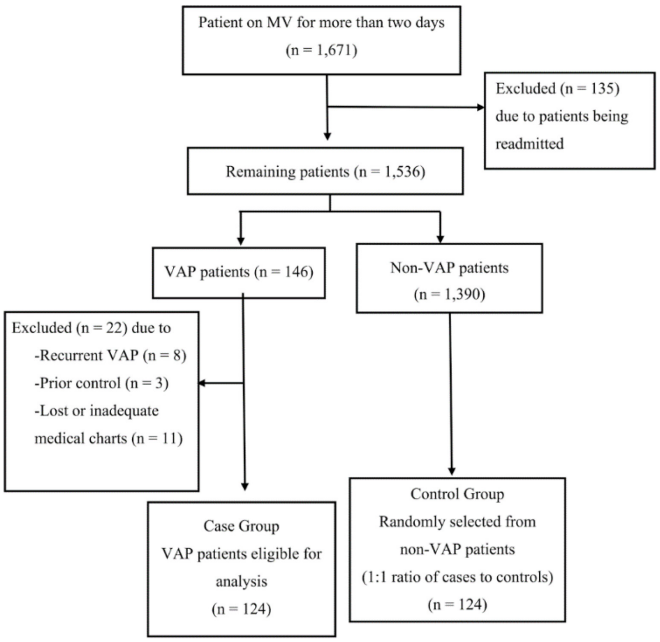
A matched case-control study nested was conducted in a cohort of patients on MV at a 650-bed, tertiary

referral hospital in Thailand. The hospital had only one combined medical-surgical ICU. The other six non-ICUs included one neurosurgical, two surgical, one neuromedical, and two medical units. The units have three types: 1 medical-surgical ICU with critically ill surgical and medical patients; 2 neurosurgical/surgical non-ICUs with either pre- or post-surgery patients; 3 neuromedical/medical non-ICUs where patients were undergoing management for conditions not sufficiently severe to warrant intensive care.

Infection control nurses prospectively identified a cohort of 1,671 patients on MV that were over age 18 years old and who required MV for at least two calendar-days. Study patients were followed through November 30, 2013, or until discharge, transfer, or death. 135 patients who were readmitted were excluded. Finally, 1,536 patients were eligible for inclusion (Figure 1).

A total of 146 VAP patients were qualified based on a definition below [9-10]. However, 22 VAP patients were excluded because they were recurrent VAP (8 patients), prior control patients (3 patients) or had lost and inadequate medical charts (11 patients). Finally, 124 VAP patients were eligible for analysis. 124 control patients were matched and randomly selected using a 1:1 (case to control ratio) according to the predefined criteria: 1 control patient's duration of MV was at least as long as the VAP patient's duration from time of intubation until onset of VAP ± 10%, and 2 start date of MV for control patient was within two calendar weeks before or after the VAP patient's start date of MV.

Figure 1. Flow diagram of patients on mechanical ventilation (MV) included in a study of risk factors for ventilator-associated pneumonia (VAP) at a hospital in Thailand.



VAP was defined as pneumonia diagnosed in patients receiving MV for more than two days, or who developed pneumonia less than two days after MV ceased. The pneumonia was diagnosed based on the following criteria: 1 a new or progressive chest infiltrate, consolidation, cavitation, or pleural effusion on chest X-ray and 2 at least two of the following conditions: 2.1 fever (> 38 ºC or > 100.4 ºF) with no other recognized cause; 2.2 leucopenia (< 4,000 WBC/mm^3) or leukocytosis (≥ 12,000 WBC/mm^3); 2.3 new onset or worsening cough, dyspnea, or tachypnea; 2.4 rales or bronchial breath sounds; 2.5 new onset of purulent sputum or change in character of sputum, increased respiratory secretions, or increased suctioning requirement; 2.6 positive growth in blood culture unrelated to previous infection; and 2.7 positive bacterial growth from respiratory secretions suctioned from endotracheal tube. The VAP was classified into either early onset (less than five days after ventilation) or late onset [11].

Clinical samples of tracheal secretion were used to detect causative bacteria. Multidrug resistant (MDR) bacteria were defined based on the European Centre for Disease Prevention and Control criteria [12]. Strains generally had to be non-susceptible to one or more agents in three or more antibiotic categories to be considered MDR. Methicillin-resistant *Staphylococcus aureus* strains were always considered MDR. For gram-negative organisms, criteria varied for Enterobacteriaceae, *Pseudomonas aeruginosa* and *A. baumannii*.

The demographic data included baseline characteristics (sex, age), underlying comorbidities, and Charlson comorbidity index score (CCS) [13] and type of patient care unit where patient received their care. And health conditions present at the time of hospital admission included: 1 compromised immune system diseases, 2 diseases causing alteration of consciousness, 3 motor vehicle accident, 4 respiratory failure, 5 infectious conditions, and 6 community acquired pneumonia.

The medication exposure variables were as follows: 1 proton pump inhibitors (PPIs), 2 antibiotic covariables: a. antibiotic (at least 1-calendar day use of intravenous antibiotics: aminopenicillin, 1st - 4th generation cephalosporins, etc.); b. number of antibiotics; c. broad spectrum antibiotic (at least 1-calendar day use of intravenous antibiotics: imipenem, 3rd or 4th generation cephalosporins, fluoroquinolone or antipseudomonal penicillin), 3 nebulizer (bronchodilator or mucolytic

agent), 4 sedative (intermittent or continuous infusion by benzodiazepine, ketamine, thiopentone, fentanyl, propofol, midazolam or lorazepam), and 5 steroid (more than 30 mg of prednisone, or equivalent, daily for three days or more). Hospital exposures at admission included: 1 prior surgery, 2 brain surgery, 3 chest/abdominal surgery, 4 emergency intubation, and 5 reintubation within 48 hours.

Data analysis

Data were analyzed using STATA software, version 12 (Statacorp LP, College Station, TX). Ventilator-associated pneumonia (VAP) rate per 1000 ventilator days (VDs) for each care unit was estimated. Matched odds ratios (mORs) were estimated by using conditional logistic regression to assess the association between baseline characteristics, underlying comorbidities, health conditions present at the time of hospital admission, type of patient care unit, receipt of medication, or hospital exposure at admission and VAP. A locally weighted scatterplot with smoothing (LOWESS) on the logit scale was used to investigate whether there was a dose-response association between age or Charlson comorbidity index score (CCS) variable and VAP. Based on the results of LOWESS curve, age was converted into a dichotomous variable using a cut of value (age ≥ 61 years *vs*. age < 61 years).

There was the collinearity between multiple variables including: type of patient care unit, prior surgery, brain surgery, chest/abdominal surgery, diseases causing alteration of consciousness, infectious conditions, and community-acquired pneumonia ($p < 0.001$). The type of patient care unit was included in the model rather than the other collinear covariates because of its greater operational importance for the hospital to identify patients who are at high risk of VAP in particular types of patient care units.

A preliminary conditional logistic regression model included variables with statistical associations in which the *p*-value was less than 0.15 plus high variability (proportion of the discordant pairs was greater than 15%). Variables that were associated with VAP in previously published studies were also included. To assess modifiable medication exposure and patient care unit, PPIs, antibiotics, nebulizers, sedatives, and patient care unit variables were included in a preliminary model regardless of statistical significance. The iterative process was used to generate the final model. There was the independent associations of VAP with the covariates when the beta coefficient of the variable of interest (PPIs, antibiotics, nebulizers, sedatives, and patient care unit variables) changes by more than 10% in the logistic regression. Finally the adjusted mORs (adj. mORs) were reported.

To compare patients with MDR and non MDR VAP, univariate logistic regressions were analyzed among a subgroup of patients. Variables in which the statistical association with MDR VAP had a *p*-value less than 0.15 were included in multivariable logistic regression analysis. A stepwise model selection method was used to determine independent effects of broad-spectrum antibiotic and type of patient care unit with MDR VAP, after adjusting for covariates. There were no missing data. The power of the study was calculated to be 98%. All statistical tests were 2-tailed at a significance of p-value < 0.05.

Ethical considerations

The control patient was randomly selected from a pool of eligible control patients with a blinded selection technique. The Institutional Review Board at the University of Illinois at Chicago and the hospital's Independent Ethics Committee of Suratthani Hospital, Thailand approved the study and waived informed consent.

Results

A total of 146 MV patients (9.5%) developed VAP, which corresponds to a rate of 10.9 VAP cases per 1,000 VDs. The neurosurgical/surgical non-ICUs had the highest rate of VAP (16.7 per 1,000 VDs), followed by medical-surgical ICU (11.1 per 1000 VDs) and neuromedical/medical non-ICUs (9.1 per 1,000 VDs) (Table 1).

Of the 146 patients with VAP, 124 (84%) were eligible for statistical analysis. 101 (81%) had at least

Table 1. Incidence of ventilator-associated pneumonia and duration on mechanical ventilation for patients in different patient care units in a Thai hospital.

Type of patient care units	VAP Patients n (%)	Patients	Days that patient was on ventilator	VAP rate (per 1,000 VD)	Rate difference (95% CI)	*p*-value
Neurosurgical/surgical non-ICUs	45 (30.8)	329	2,684	16.7	5.6 (-1.1–12.4)	0.056
Neuromedical/medical non-ICUs	79 (54.1)	985	8,666	9.1	-2.0 (-7.0–3.0)	0.204
Medical-surgical ICU	22 (15.1)	222	1,978	11.1	Reference	
Total	146	1,536	13,328	10.9		

VDs: ventilator days; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia.

one bacterial isolate from a tracheal aspirate culture. Of these patients with tracheal cultures, 40% (n = 41) were polybacterial VAP. 60% (n = 61) of the isolated 132 bacterial strains from the patient tracheal cultures that were plausibly considered VAP had MDR bacteria. Of the 132 isolations, 128 (97%) were gram-negative bacteria and 84 (63.6%) were MDR bacteria. The most isolated bacteria were *A. baumannii* (n = 51, 38.6 %) and *Klebsiella pneumoniae* (*K. pneumoniae*) (n = 47, 35.6%). Among these organisms, MDR bacteria was common, particularly in *A. baumannii* and *K. pneumoniae,* where MDR prevalence was 82.4% and 61.7%, respectively (Table 2). The median time from intubation until development of VAP was six days, with an interquartile range of four to eight days.

Bivariate analyses showed no differences in gender and age between VAP and control patients. Patients with severe renal disease or chronic obstructive pulmonary disease (COPD) were statistically significant less common in patients with VAP compared to control patients (mOR, 0.3 [0.1–0.9], p = 0.026 and 0.4 [0.2–0.9], p = 0.0035, respectively). Among health conditions present at the time of hospital admission, diseases causing an alteration of consciousness had a statistically significant association with VAP (mOR = 3.1, 1.6–6.1, p = 0.001) (Table 3).

There were no statistically significant differences in the risk of developing VAP between the medical-surgical ICU and neurosurgical/surgical non-ICUs or neuromedical/medical non-ICUs. However, the risk of developing VAP was lightly greater in the non-intensive care surgical units than it was in the medical-surgical ICU (adj. mOR = 1.9, 0.6-6.4, p = 0.278).

Table 2. Number and percentage of tracheal samples with multidrug resistant bacteria among the ventilator-associated pneumonia pathogens from patients receiving mechanical ventilation at a Thai hospital.

Bacteria (Number of isolates)	Number of isolates with MDR (%)
Acinetobacter baumannii (51)	42 (82.4)
Klebsiella pneumoniae (47)	29 (61.7)
Pseudomonas aeruginosa (22)	8 (36.4)
Enterobacter cloacae (5)	3 (60.0)
Staphylococcus aureus (4)	1 (25.0)
Escherichia coli (3)	1 (33.3)
Total (132)	84 (63.6)

Patients in the surgical ICU were more likely to develop VAP than patients in the non-surgical ICU (adj. mOR = 2.4, 1.0-5.6, p = 0.04). There was a strong association between VAP and treatment in neurosurgical/surgical non-ICUs. We hypothesized that this association was likely related to brain surgery or conditions that led to treatment in those units. Having brain surgery and prior surgery were strongly associated with VAP (mOR = 2.7, 1.3–-5.4, p = 0.003 and 2.7, 1.1–-6.4, p = 0.019, respectively) (Table 4).

There was a statistically significant association between receiving PPIs and developing VAP (mOR = 2.7, 1.6–4.6, p < 0.001). In contrast, this study found that taking any antibiotic (mOR = 0.4, 0.2–0.9, p = 0.016) or a broad-spectrum antibiotic (mOR = 0.5, 0.2–0.9, p = 0.021) were highly protective factors against developing VAP. Of the 248 patients, 84% received at least one antibiotic (n = 208), 73% received a broad-spectrum antibiotic (n = 181) and 38% (n = 95) received multiple antibiotics (2-4 types of antibiotics) (Table 4).

Table 3. Prevalence of baseline characteristics of patients with ventilator-associated pneumonia compared to control patients in study of patients on mechanical ventilation in a Thai hospital(n = 248).

	VAP patients n = 124; N (%)	Control patients n = 124; N (%)	MOR (95% CI)	p-value
Female	60 (48%)	58 (47%)	1.1 (0.6–1.8)	0.789
Over 60 years of age	80 (64)	82 (66)	0.9 (0.5–1.6)	0.782
Median (IQR) of age (years)	69 (50-80)	69 (49-81)		0.665
Underlying comorbidities				
Severe renal disease	6 (5)	16 (13)	0.3 (0.1–0.9)	0.026*
Chronic obstructive pulmonary disease	10 (8)	21 (17)	0.4 (0.2–0.9)	0.035*
Hemiplegia	14 (11)	23 (18)	0.5 (0.3–1.1)	0.109
Diabetes	15 (12)	23 (18)	0.5 (0.3–1.2)	0.158
Median (IQR) of Charlson comorbidity index score (points)	4 (2-5.5)	5 (3-7)		0.713
Health conditions present at the time of hospital admission				
Compromised immune system diseases	10 (8)	16 (13)	0.6 (0.3–1.4)	0.221
Diseases causing alteration of consciousness	43 (35)	20 (16)	3.1 (1.6–6.1)	0.001*
Motor vehicle accident	12 (10)	8 (6)	1.6 (0.6–4.6)	0.317
Respiratory failure	11 (9)	19 (15)	0.6 (0.3–1.2)	0.144
Infectious condition	6 (5)	8 (6)	0.7 (0.2–2.2)	0.564
Community-acquired pneumonia	29 (23)	39 (31)	0.6 (0.4–1.2)	0.149

mOR: matched odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; IQR: interquartile range; *: p-value < 0.05.

Table 4. Prevalence of risk factors for ventilator-associated pneumonia (VAP) among VAP and control patients and bivariate analysis of association between different risk factors and VAP in a Thai hospital(n= 248).

Variables	VAP patients n = 124; N (%)	Control patients n = 124; N (%)	mOR (95% CI)	*p*-value
Types of patient care unit				
Neurosurgical/surgical non-ICUs	45 (36)	18 (14)	2.4 (0.8–7.1)	0.112
Neuromedical/medical non-ICUs	66 (53)	96 (77)	0.6 (0.2–1.4)	0.225
Medical-surgical ICU	13 (11)	10 (8)	Reference	
Receipt of medications				
Proton pump inhibitor	85 (68)	52 (42)	2.7 (1.6–4.6)	< 0.001*
Antibiotics	97 (78)	111 (89)	0.4 (0.2–-0.9)	0.016*
Number of antibiotics				
2-4 antibiotics	50 (40)	45 (36)	0.4 (0.1–1.3)	0.109
1 antibiotic	47 (38)	66 (53)	0.4 (0.2–1.1)	0.074
No antibiotics	27 (22)	13 (11)	Reference	
Broad spectrum antibiotics	83 (67)	98 (79)	0.5 (0.2–0.9)	0.021*
Nebulizers	66 (53)	76 (61)	0.6 (0.3–1.1)	0.122
Sedatives	57 (46)	47 (38)	1.4 (0.8–2.2)	0.211
Steroids	4 (3)	9 (7)	0.4 (0.1–1.4)	0.150
Hospital exposures at admission				
Prior surgery	39 (31)	20 (16)	2.7 (1.3–-5.4)	0.003*
Brain surgery	21 (17)	9 (7)	2.7 (1.1–6.4)	0.019*
Chest/abdominal surgery	12 (9)	7 (5)	1.7 (0.7–4.3)	0.251
Emergency intubation	110 (88)	116 (93)	0.5 (0.2–1.3)	0.179
Reintubation	28 (23)	26 (21)	1.1 (0.6–2.1)	0.745

mOR: matched odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; *: *p*-value < 0.05.

Table 5. Crude and adjusted matched odds ratios for association between risk factors and ventilator-associated pneumonia (VAP) among VAP and control patients in a Thai hospital(n = 248).

Risk factors	Bivariate analyses		Multivariate analyses	
	mOR (95% CI)	*p*-value	Adjusted mOR (95% CI)	*p*-value
Proton pump inhibitors	2.7 (1.6–4.6)	<.001	2.2 (1.2–4.2)	0.011*
Antibiotics	0.4 (0.2–0.9)	0.016	0.4 (0.2–1.0)	0.054
Nebulizers	0.6 (0.3–1.1)	0.122	0.7 (0.3–1.6)	0.459
Sedatives	1.4 (0.8–2.2)	0.211	1.2 (0.7–2.2)	0.528
Neurosurgical/surgical non-ICUs	2.4 (0.8–7.1)	0.112	1.9 (0.6–6.4)	0.278
Neuromedical/medical non-ICUs	0.6 (0.2–1.4)	0.225	0.8 (0.3–2.2)	0.614
Medical-Surgical ICU	Reference		Reference	
Over 60 years of age	0.9 (0.5–1.6)	0.782	2.4 (1.0–5.9)	0.045*
Charlson comorbidity index score (points)	0.9 (0.8–0.9)	0.036	0.9 (0.7–1.0)	0.115
Reintubation	1.1 (0.6–2.1)	0.745	NA	NA

mOR: matched odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; NA: not available; *: *p*-value < 0.05.

Table 6. Prevalence of baseline characteristics among patients with multidrug resistant (MDR) ventilator-associated pneumonia (VAP) compared to patients with non MDR VAP in a Thai hospital(n = 101).

Variables	MDR VAP patients, n = 61	Non MDR VAP patients, n = 40	cOR (95% CI)	*p*-value
Late onset VAP	45 (74)	25 (62)	1.7 (0.7–3.9)	0.232
Female	41 (67)	10 (25)	6.1 (2.5–15.0)	<0.001*
Over 60 years of age	45 (74)	23 (57)	2.1 (0.9–4.8)	0.091
Median (IQR) age (years)	72 (55-80)	66 (41-79)		0.208
Underlying comorbidities				
Severe renal disease	1 (2)	3 (7)	0.2 (0.1–2.0)	0.178
Chronic obstructive pulmonary disease	5 (8)	4 (10)	0.8 (0.2–3.2)	0.756
Hemiplegia	8 (13)	5 (12)	1.0 (0.3–3.5)	0.928
Diabetes	10 (16)	4 (10)	1.8 (0.5–6.1)	0.368
Median (IQR) of Charlson comorbidity index score (points)	5 (3-6)	4 (1-5)		0.076
Health conditions present at the time of hospital admission				
Compromised immune system diseases	1 (2)	4 (7)	2.7 (0.3–25.4)	0.336
Diseases causing alteration of consciousness	14 (23)	23 (57)	0.2 (0.1–0.5)	<0.001*
Motor vehicle accident	7 (11)	5 (12)	0.9 (0.3-3.1)	0.876
Respiratory failure	5 (8)	3 (7)	1.1 (0.2-4.9)	0.898
Infectious condition	4 (6)	0 (0)	NA	NA
Community-acquired pneumonia	18 (29)	5 (12)	2.9 (1.0–8.7)	0.039*

cOR: crude odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; IQR: interquartile range; NA: not available; *: *p*-value < 0.05.

Specifically, third and fourth generation cephalosporins (71%) were the most commonly received, followed by fluoroquinolone (17%) and carbapenems (14%).

In the final model, after controlling for the patient care unit, CCS, and age group, the receipt of PPIs was a strong risk factor for developing VAP (adj. mOR = 2.2, 1.2–4.2, $p = 0.011$). Yet, the receipt of an antibiotic was a preventive factor for VAP (adj. mOR = 0.4, 0.2–1.0, $p = 0.054$) (Table 5).

A subgroup analysis comparing patients with MDR VAP and non MDR VAP showed those with MDR VAP were more likely to be female (cOR = 6.1, 2.5–15.0, $p < 0.001$), have a community acquired pneumonia (cOR = 2.9, 1.0–8.7, $p = 0.039$), receive an antibiotic (cOR = 5.7, 2.1–15.6, $p = 0.001$), a broad-spectrum antibiotic (cOR = 10.6, 4.1–27.1, $p < 0.001$), or a nebulizer (cOR = 6.1, 2.5–15.0, $p < 0.001$). Patients with MDR VAP were less likely to have a disease causing an alteration of consciousness (cOR = 0.2, 0.1–0.5, $p < 0.001$) before VAP onset, be treated in neurosurgical/surgical non-ICUs (cOR = 0.1, 0.01-0.9, $p = 0.047$) compared to the medical-surgical ICU, or undergo brain surgery (cOR = 0.1, 0.03-0.4, $p < 0.001$). There was no association between late onset VAP and MDR VAP (Tables 6 and 7). In multivariable analyses, being female (adj. OR = 6.3, 1.9–20.4, $p = 0.002$) and receiving broad-spectrum antibiotics (adj. OR = 14.9, 3.0–28.0, $p < 0.001$) were statistically significant associated with MDR VAP, after adjusting for age group and CCS (Table 8).

Table 7. Prevalence of risk factors for multidrug resistant pneumonia (MDR VAP) among MDR VAP and non MDR VAP patients (n = 101) in a Thai hospital.

Variables	MDR VAP patients, n = 61	Non MDR VAP patients, n = 40	cOR (95% CI)	*p*-value
Types of patient care unit				
Neurosurgical/surgical non-ICUs	16 (26)	25 (63)	0.1 (0.01–0.9)	0.047*
Neuromedical/medical non-ICUs	39 (64)	14 (35)	0.5 (0.05–4.2)	0.495
Medical-Surgical ICU	6 (10)	1 (2)	Reference	
Receipt of medications				
Proton pump inhibitor	40 (65)	30 (75)	0.6 (0.3–1.5)	0.317
Antibiotic	54 (88)	23 (57)	5.7 (2.1–15.6)	0.001*
Number of antibiotics				
2-4 antibiotic	31 (51)	9 (22)	8.3 (2.6–26.4)	< 0.001*
1 antibiotic	23 (38)	14 (35)	3.9 (1.3–12.0)	0.014*
No antibiotic	7 (11)	17 (43)	Reference	
Broad spectrum antibiotics	50 (82)	12 (30)	10.6 (4.1–27.1)	< 0.001*
Nebulizers	41 (67)	10 (25)	6.1 (2.5–15.0)	< 0.001*
Sedatives	26 (43)	18 (45)	0.9 (0.4-2.0)	0.814
Steroids	1 (2)	1 (3)	0.6 (0.04-10.7)	0.761
Hospital exposures at admission				
Prior surgery	17 (28)	18 (45)	0.5 (0.2–1.1)	0.079
Brain surgery	4 (7)	14 (35)	0.1 (0.03–0.4)	< 0.001*
Chest/abdominal surgery	8 (13)	3 (8)	1.9 (0.5–7.5)	0.381
Emergency intubation	53 (87)	35 (87)	0.9 (0.3–3.1)	0.928
Reintubation	14 (23)	9 (22)	1.0 (0.4–2.6)	0.958

cOR: crude odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; *: *p*-value < 0.05.

Table 8. Crude and adjusted odds ratios for association between risk factors and multidrug resistant ventilator-associated pneumonia (MDR VAP) among MDR VAP and non MDR VAP patients in a Thai hospital (n = 101).

Risk factors	Bivariate analyses		Multivariate analyses	
	cOR (95% CI)	*p*-value	Adj.OR (95% CI)	*p*-value
Female	6.1 (2.5–15.0)	< 0.001*	6.3 (1.9–20.4)	0.002*
Broad spectrum antibiotics	10.6 (4.1–27.1)	< 0.001*	14.9 (3.0–28.0)	< 0.001*
Neurosurgical/surgical non-ICUs	0.1 (0.01–0.9)	0.047	0.2 (0.01–2.1)	0.179
Neuromedical/medical non-ICUs	0.5 (0.05–4.2)	0.495	0.8 (0.07–9.0)	0.865
Medical-Surgical ICU	Reference		Reference	
Over 60 years of age	2.1 (0.9–4.8)	0.088	1.4 (0.2–9.5)	0.726
Charlson comorbidity index score (points)	1.2 (0.9–1.4)	0.055	1.0 (0.7–1.4)	0.898
Nebulizers	6.1 (2.5–15.0)	< 0.001*	NA	NA

cOR: crude odds ratio; adj.OR: adjusted odds ratio; CI: confidence interval; ICU: intensive care unit; VAP: ventilator-associated pneumonia; NA: not available; *: *p*-value < 0.05.

Discussion

The study assessed factors associated with VAP among patients on MV in ICU and non-ICU settings. The results revealed patients in the neurosurgical/surgical non-ICUs had the highest incidence of VAP. The receipt of PPIs was an independent risk factor for VAP, whereas the receipt of antibiotics was an independent protective factor. Furthermore, broad-spectrum antibiotics had a statistically significant association with MDR VAP. The most common pathogen was MDR *A. baumannii*.

One explanation for these differences in VAP risk is patients treated in neurosurgical/surgical non-ICUs are more likely to experience alterations of consciousness or brain surgery than in the other settings. Alterations of consciousness or brain surgery were associated with VAP. The finding suggests that the patients in the neurosurgical/surgical non-ICUs, and those who have an alteration of consciousness or brain surgery are at greatest risk of VAP. We hypothesize that the increased risk of VAP is due to decreased bowel motility and subsequent colonization with pathogenic bacteria [14], placement in a supine position, feeding through an oro- or nasogastric tube [15], and intubation in emergency conditions outside the operating room [16]. Therefore, the hospital should emphasize specific strategies to prevent VAP in neurosurgical/surgical non-ICUs.

Patients with altered consciousness may benefit from short-term antibiotic prophylaxis. A seven-year observational study of 175 patients with severe traumatic brain injury showed incidence of VAP was 47.4 per 1000 VDs. Administering prophylactic antibiotics was a protective factor against early onset VAP (adj.OR = 0.3, 0.1–0.8) after adjusting for injury severity score [17]. A randomized controlled trial among patients with structural coma found statistically significant decreased incidences of VAP and early onset VAP between the prophylaxis and control groups (VAP: 24 % and 50%, $p = 0.007$; early onset VAP: 16% and 36%, $p = 0.02$, respectively) [18]. Another randomized controlled trial among coma patients showed that administration of short-course intravenous antibiotic provided an effective prophylactic strategy reducing incidence of early onset VAP (2.8% and 22.4%, $p < 0.01$) [19].

Spain VAP prevention guidelines recommend a short course (2-3 days) intravenous cephalosporin (cefuroxime, ceftriaxone) or amoxicillin-clavulanate for patients with an alteration of consciousness [20]. Guideline-driven prophylaxis, however, may increase risk of infection with MDR bacteria. A prospective cohort study compared the incidence of VAP between two neurosurgical and trauma ICUs using an aggressive or conservative approach. Results showed similar incidences of VAP between the ICUs (49.3 and 39.8 per 1,000 VDs, $p = 0.16$). But the prevalence of MDR bacteria was much higher with the aggressive approach (38.2% and 9.9%, $p < 0.001$) [21]. These findings support the link between the aggressive use of antibiotics and development of resistant bacteria. Therefore, medical providers should consider this potential outcome when prescribing antibiotic prophylaxis.

Likewise, data from two university hospitals in Thailand demonstrate that more than 50% of patients with VAP have MDR bacterial infections. Of those with *A. baumannii* VAP, 82.7-90.2% are MDR *A. baumannii* [5,22]. These results may be explained by environmental climate, since unlike ICUs, all of Thailand non-ICUs do not air conditioning. Gram-negative bacteria, especially *A. baumannii,* colonize more rapidly in warm and humid regions. Our results with more than 80% of *A. baumannii* resistant to usual gram-negative antibiotics are consistent with the increased incidence of MDR *A. baumannii* over the last decade.

The lack of an association of MDR and late onset VAP in our study may be due to low statistical power. It also be explained by the fact that some patients were transferred from other hospitals without our knowledge. This situation may lead to differential misclassification of these patients from other hospitals with late onset VAP (with hospital days from another hospital) as early onset VAP. This misclassification would attenuate the odd ratio. However, the finding suggests that in this hospital, choice of empiric antibiotic therapy should not be guided by early or late VAP occurrence, but rather on the bacteriology and susceptibility pattern present in each hospital unit.

PPIs are commonly used to prevent stress ulcers in ICU patients. Available evidence suggests that PPIs are superior to Histamine-2 receptor antagonists (H2RAs) and sucralfate in protecting critically ill patients against gastrointestinal bleeding [23]. A meta-analysis and a guideline both suggest that prophylactic treatment for patients at high risk of bleeding with PPIs and H2RAs are likely to reduce bleeding compared with no prophylaxis [23-24]. There is little data comparing the effectiveness of these medications in reducing bleeding specifically in patients treated in neurosurgical non-ICUs [25]. Further prospective research is needed to confirm whether these medications successfully prevent bleeding for these patients [26]. Our study

shows that PPIs might harm the patients because the PPI is associated with a heightened risk of VAP [27]. Large clinical trials are necessary to resolve uncertainties about the risk-benefit of using PPIs to stress ulcer prophylaxis for neurosurgical patients.

Like other research studies [28-29], we found no association between the use of a nebulizer and VAP. However, some studies demonstrated an enhanced risk of VAP associated with nebulizer treatments. One study reported that humidifier water (HW) or heat and moisture exchanger (HME) might be a source of VAP because bacterial isolates from HW-HME filter were of the same pattern as those found in VAP patients [30]. Two studies demonstrated an increased risk of VAP with receipt of nebulization treatment due to the high proportion of patients with COPD in the study samples [31-32]. In contrast, only 8% of our patients had a COPD diagnosis. There is also currently a randomized control trial study in progress that is investigating whether nebulization of bronchodilator prevents VAP [33].

Sedatives protect patients with brain injury from development of edema or ischemia [34], reduce stress of respiratory failure [35]. Yet, sedatives may predispose patients to develop of VAP by decreasing cough reflex, reducing endotracheal secretion clearance, or impairing gut motility [9]. However, evidence is limited and unclear due to inconsistency in how light sedation is defined [36]. The Society of Critical Care Medicine recommends light sedation for patients receiving MV [37]. Moreover, providing MV patients with an optimal level of sedation is challenging [38]. A randomized controlled trial showed lower incidences of VAP in patients in a non-sedation group compared to those in the sedation group with daily interruptions (VAP incidence: 23% and 46%, respectively, $p < 0.05$) [39]. We found no association between sedatives and VAP (mOR = 1.4, 0.8–2.2). As noted, patients at the highest risk of VAP had undergone brain surgery or impaired consciousness; therefore, sedation induced by undergoing brain surgery would decrease sedative use.

The study has several limitations: 1 Since patients admitted to the ICU and non-ICUs may have different severities, and there was a lack of oxygen saturation measurements (e.g., arterial pH, partial pressure of CO_2) in patients from non-ICU settings, preventing use of a severity illness index. 2 The VAP definition used in our study is the outdated definition. 3 The hospital has only one ICU; therefore, the number of VAP patients in ICU was limited. 4 This study did not utilize microbiological confirmation for VAP diagnosis. These methods, however, are rarely used in studies of VAP. There is no "gold standard" method that exists to diagnose VAP [40]. 5 An additional limitation was low statistical power to detect a significant association between MDR VAP patients and additional uncontrolled confounders that were not accounted for.

The study has three advantages: 1. The matching design might control more efficiently for the confounding effect of MV duration [8,41] than only using statistical regression analysis. 2. A matched case-control study nested in a cohort of patients on mechanical ventilation yields an odds ratio that approximates the risk ratio obtained from a classic cohort study. Because of the data abstraction only among VAP and matched control patients, not the entire cohort, the labor reduction is especially advantageous for hospitals using paper records. 3. This study adds to the sparse literature on VAP in resource-constrained areas. One unique aspect of this study is the risk comparison of VAP in ICU and non-ICU settings, which is important in countries delivering MV in less intense step-down-type units.

Conclusions

In adult patients on MV, the use of proton pump inhibitors (PPIs) and being treated in neurosurgical/surgical non-ICUs was associated with increased risk of developing VAP. Infection control interventions related to ventilator care and evidence-based guidelines for prescribing PPIs should be considered, particularly among patient on MV in neurosurgical/surgical non-ICU settings.

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