Microorganisms and Clinical Outcomes of Early- and Late-onset Ventilator-associated Pneumonia at Srinagarind Hospital, a Tertiary Center in Northeastern Thailand

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Research article

Keywords: Early-onset VAP, Late-onset VAP, Microbiology, Outcome, Mortality

DOI: https://doi.org/10.21203/rs.3.rs-37041/v1

Abstract

Back ground: Ventilator-associated pneumonia (VAP) isacommon nocosomial infection inintensive care unit (ICU). Local microbiological surveillance of pathogens and resistance patternsfor early-onset VAP (EOVAP) and late-onset VAP (LOVAP)will help to choose appropriate empiric antibiotics.

Objective: To comparethe multi-drug resistant (MDR) pathogens, treatment outcomes,and factors associated with hospital mortality of VAP.

Method:A cross-sectional studybetween 1 January 2015 and 31 December 2017 at Srinagarind hospital, KhonKaen University was conducted. The demographic data, causative pathogens, hospital length of stay (LOS), ICU LOS, mechanical ventilator (MV) days, and hospital mortality were retrospectively reviewed.

Results: One hundred and ninety patients were enrolled; 42 (22%) were EOVAP and 148 (78%) were LOVAP. *Acinetobacterbaummanii* was the most common pathogen in both groups (50 % EOVAP vs 52.7% LOVAP). MDR pathogens were significant greater in LOVAP (81.8 %) than EOVAP (61.9%) (p = 0.007). The EOVAP had a significantly better ICU LOS (median 20.0 (11.0, 30.0) *vs*. 26.5 (17.0, 43.0) days), hospital LOS (median 26.5 (15.0, 44.0) *vs*. 35.5 (24.0, 56.0) days) shorter MV days (14.0 (10.0, 29.0) *vs*. 23.0 (14.0, 35.5) days) and lowerhospital mortality (11.9 % VS 27.7%) than LOVAP (p< 0.05). The factor associated with hospital mortality washavingsimplified acute physiology score (SAP)≥ 40 with an adjustedodds ratio(aOR) of 2.22 (95%CI, 1.08-4.54,p = 0.02).

Conclusion: LOVAP had significantly higherMDR pathogens, MV days, ICU LOS, hospital LOS andhospital mortality than EOVAP. A broad-spectrum antibiotic to cover MDR pathogensshould be considered in LOVAP.The factor associated with hospital mortality of VAP was a SAPII score ≥ 40.

Background

Pneumonia is the most common hospital-acquired infection with a prevalence of approximately 22%[1, 2]. Ventilator-associated pneumonia (VAP) is pneumonia developing after 48–72 hours of endotracheal intubation[3, 4]. VAP is the most common nosocomial infection, developed in about 9–27% of mechanically ventilated patients[5, 6]. Data from the International Nosocomial Infection Control Consortium (INICC) collected summary data from 50 countries including Southeast Asia during 2010–2015 indicated the VAP rate was 13.1 per 1000 mechanical ventilator-days in the medical and surgical intensive care unit (ICU)[7]. Similar results of Reechaipichitkul et al who determined that VAP rates in Srinagarind Hospital, Khon Kaen University, a tertiary-care hospital in northeastern Thailand were 13.6 and 12.6 per 1000 mechanical ventilator-days in 2008 and 2009. This study also demonstrated that more than half of the costs of nocosomial treatment in 2008 and 2009 were the costs for hospital acquired pneumonia (HAP) and VAP, 16.8 and 17.5 million Baht[8]. Melsen WG et al performed a meta-analysis and suggested that overall attributable mortality in mechanical ventilator patients from VAP was 13%[9].

VAP was categorized into early-onset VAP (EOVAP) and late-onset VAP (LOVAP) depending upon when it occurred on which days after hospitalization. The cutoff point of a range 4–7 days onset varied across the studies[10–15]. Recent guideline for HAP and VAP management from The Infectious Disease Society of America (IDSA)/American Thoracic Society(ATS) and the International ERS/ESICM/ESCMID/ALAT use the cutoff point of 5 days after hospitalization[2, 16, 17]. It is believed that in EOVAP, the causative pathogen was not drug-resistant bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, antibiotic-sensitive enteric gram-negative bacilli or methicillin-sensitive *Staphylococcus aureus* (MSSA). There is a greater risk that the causative organisms in LOVAP are multidrug-resistant (MDR) such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), extended-spectrum beta-lactamase-producing bacteria (ESBL) and other gram-negative bacilli[16, 18, 19]. The prevalence of MDR pathogens between EOVAP and LOVAP in several studies remained a controversy. Several studies demonstrated that EOVAP had a significantly lower prevalence of MDR pathogens[20–22]. Subsequent studies, however, did not show a significant difference in MDR pathogens between EOVAP and LOVAP groups[10, 11, 13, 23].

Therefore, the study was conducted and aimed to compare the pathogens, clinical characteristics, treatment outcomes between EOVAP and LOVAP groups, and factors associated with hospital mortality.

Methods

A cross-sectional study was conducted at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University which is a 1466-bed tertiary care center in Northeast Thailand. The study was approved by the Human Research Ethics Committee, Khon Kaen University (approval number HE611281). All VAP patients recorded by the infectious control (IC) unit from January 1, 2015, to December 31, 2017, were enrolled.

Study subjects

VAP was diagnosed by the following criteria: 1) a pulmonary infection occurring 48 hours after mechanical ventilation 2) new pulmonary infiltration on chest radiograph 3) at least two of the three following characteristics: temperatures > 38.3 °C or < 36.5 °C, purulent tracheal secretions, and leukocytosis (white blood cell > 12,000 cells/mm^3) or leukopenia (white blood cell < 4,000 cells/mm^3) [4, 24]. The exclusion criteria were as following: 1) patients who had previous abnormal chest imaging including pulmonary edema, adult respiratory distress syndrome, pulmonary embolism, alveolar hemorrhage, pulmonary tuberculosis, and recent pneumonia 2) Immunocompromised patients who received any immunosuppressive agents, chemotherapy, or prednisolone equivalence ≥ 15 mg/day

Data collection

The medical records of demographic data, hospital department, laboratory results, chest radiological findings, microbiological profiles, tracheostomy tube placement, hospital length of stay (LOS), intensive care unit (ICU) LOS, mechanical ventilator (MV) days and hospital mortality were reviewed.

Definition and outcome

EOVAP defined as VAP developed before 5 calendar days of hospitalization while LOVAP was VAP occurred at least 5 calendar days of hospitalization. Multi-drug resistant (MDR) bacteria were defined as organisms that resisted al least 3 classes of antibiotics[25]. MDR pathogens included extended-spectrum beta-lactamase-producing (ESBL) bacteria, carbapenem-resistant enterobacteriaceae (CRE), MRSA, and other MDR bacteria that were reported from the microbiological laboratory. The causative organisms were defined as one or more of the following: 1) an isolated organism from hemoculture 2) an isolated organism from pleural effusion 3) an isolated numerous growth organism on a semiquantitative method or isolated organism on the quantitative method i.e. endotracheal aspirate $> 10^5$ colony forming unit (CFU)/ml, bronchoalveolar lavage $> 10^4$CFU/ml or protected specimen brush $\geq 10^3$ CFU/ml. Hospital mortality was death occurring during the same admission of VAP diagnosis.

The primary oucome was to compare the MDR pathogen between EOVAP and LOVAP. The secondary outcome was to compare causative pathogens, hospital length of stay (LOS), ICU LOS, mechanical ventilator (MV) days, and hospital mortality between EOVAP and LOVAP.Factors associated hospital mortality of VAP were identified .

Statistical analysis

The categorical data were shown as numbers and percentages. The normal distributed continuous data were presented as mean and standard deviation (SD) while the non-normal distributed data were presented as the median and interquartile range (IQR). A comparison of category data used the Chi-square test and Fisher's exact test depending on data. The nonparametric data used the Mann-Whitney U test for comparison. The factors associated with hospital mortality in VAP subjects were evaluated by univariate logistic regression analysis. The stepwise backward multiple logistic regression analysis of factors with a p-value < 0.2 on univariate analysis or factors with previous reports of clinical significance was performed. Crude odds ratio (cOR) and adjusted odds ratio (aOR) with their 95% confidence intervals (95% CI) were demonstrated. A p-value of less than 0.05 was considered statistically significant The statistical analysis was performed by Stata version 10.1(StataCorp, Texas, USA).

Results

Patients

During the study period, 190 patients were diagnosed as VAP. Forty-two patients were EOVAP and 148 patients were LOVAP. The mean (SD) age of these was 64.3 (16.2) years. Males were 127 (66.8%) and females were 63 (33.2%). One hundred and seven subjects were admitted to the Medicine Department (96 medical ICU and 11 general medicine ward). Eighty-three subjects were admitted to the Surgical Department (73 surgical ICU and 10 general surgery ward). One hundred and forty-eight patients had an underlying disease. The common underlying diseases were hypertension (41.6%), diabetes mellitus

(27.4%), cardiovascular disease (26.8%). The mean (SD) of the simplified acute physiology score (SAP) II score was 43.7 (13.3). Lobar pneumonia was the most common finding on chest radiography (75.8%). Pleural effusion developed in 28.4% of all subjects. The demographic data of EOVAP and LOVAP patients were shown in Table 1. LOVAP patients had a higher mean age and more comorbidities than EOVAP patients while the chest radiographic findings were similar between groups.

Table 1
Demographic data of early-onset VAP (n = 42) and late-onset VAP (n = 148)

Characteristics	Early-onset VAP n (%)	Late-onset VAP n (%)
Mean age in years (SD)	58.5 (16.9)	65.9 (15.7)
Male	34 (81)	93 (62.8)
Ward	5 (55.6)	23 (79.3)
Medical ICU	14 (33.3)	82 (55.4)
Surgical ICU	21 (50.0)	52 (35.1)
General medicine ward	3 (7.1)	8 (5.4)
General surgery ward	4 (9.5)	6 (4.1)
Underlying diseases	28 (66.7)	120 (81.1)
Hypertension	17 (40.5)	62 (41.9)
Diabetes mellitus	10 (23.8)	42 (28.4)
Cardiovascular disease	11 (26.2)	40 (27.0)
Renal failure	4 (9.5)	37(25.0)
Neurological disease	6 (14.3)	22 (14.9)
Dyslipidemia	4 (9.5)	17 (11.5)
Lung disease	6 (14.3)	13 (8.8)
Gastrointestinal disease	2 (4.8)	11(7.4)
Other	1 (2.4)	17 (11.5)
Hospitalized within 90 days	4 (9.5)	10 (6.8)
Antibiotic therapy in the prior month	22 (52.4)	101 (68.2)
Mean SAPII score (SD)	40.9 (14.1)	44.4 (12.9)
Chest radiographic finding		
Lobar pneumonia	34 (80.9)	111 (75.0)
Multilobar pneumonia	8 (19.0)	37 (25.0)
Pleural effusion	12 (28.6)	42 (28.4)

SD = standard deviation; ICU = intensive care unit, IQR = interquartile range

Primary outcomes

The causative organisms were mostly gram-negative bacteria (97.4%) while gram-positive bacteria were isolated 2.6%; 4.8% of EOVAP and 2.0% of LOVAP. The most common pathogens were *Acinetobacter baumannii* (52.1%), *Klebsiella pneumoniae* (15.3%), *Stenotrophomonas maltophilia* (13.2%), *Pseudomonas aeruginosa* (8.9%). The MDR pathogens were identified 77.4%; 3.7% of ESBL producing organism, 5.3% of CRE, 1.6% of MRSA and 66.8% of other MDR gram-negative organisms. The overall MDR bacteria were found 61.9% in the EOVAP while in LOVAP were 81.8%. The LOVAP had significantly more MDR pathogens than EOVAP ($p = 0.007$). For MDR pathogens, the ESBL producing organisms were found in 2.4% of EOVAP and 4.1% of LOVAP. The CRE was found at 2.4% in EOVAP and 6.1% in LOVAP. The proper empiric antibiotics were used to treat 130 (68.4%) study subjects; 61.9% of EOVAP and 70.3% of LOVAP. The percentage of proper empiric treatment was similar between groups ($p = 0.30$). (Table 2)

Table 2
Microorganisms identified in early-onset VAP (n = 42) and late-onset VAP (n = 148)

Microorganism	Early-onset VAP n (%)	Late-onset VAP n (%)	p-value
Gram-negative organism	40 (95.2)	145 (97.9)	0.31
Acinetobacter baumannii	21 (50.0)	78 (52.7)	0.76
MDR *Acinetobacter baumannii*	20 (47.6%)	73 (49.3)	0.84
Klebsiella pneumoniae	8 (19.0)	21 (14.2)	0.44
MDR *Klebsiella pneumoniae*	1 (2.4)	18 (12.2)	0.64
ESBLs-*Klebsiella pneumoniae*	0 (0.0)	5 (3.4)	0.07
CRE *Klebsiella pneumoniae*	1 (2.4)	9 (6.1)	0.17
Pseudomonas aeruginosa	3 (7.1)	14 (9.5)	0.24
MDR *Pseudomonas aeruginosa*	1 (2.4)	2 (1.4)	0.31
Stenotrophomonas maltophilia	2 (4.8)	23 (15.5)	0.64
MDR *Stenotrophomonas maltophilia*	2 (4.8)	22 (14.9)	0.33
Enterobacter spp.	2 (4.8)	2 (1.4)	0.007*
MDR *Enterobacter spp.*	1 (2.4)	2 (1.4)	
ESBLs-*Enterobacter spp.*	1 (2.4)	1 (2.4)	
Other gram-negative organisms	4 (1.7)	7 (4.73)	
Gram-positive organism	2 (4.8)	3 (2.0)	
	1 (2.4)	2 (1.4)	
	1 (2.4)	2 (1.4)	
	1 (2.4)	1 (0.7)	
	26 (61.9)	121 (81.8)	

*p-value < 0.05

ESBLs = extended-spectrum beta-lactamase-producing bacteria, CRE = carbapenem-resistant enterobacteriaceae, MRSA = methicillin-resistant *Staphylococcus aureus*

** Multidrug-resistant pathogens included ESBLs, CRE, MRSA, and other MDR organisms

Microorganism	Early-onset VAP n (%)	Late-onset VAP n (%)	p-value
Staphylococcus aureus MRSA Other gram-positive organisms Multidrug-resistant pathogens**			
*p-value < 0.05			
ESBLs = extended-spectrum beta-lactamase-producing bacteria, CRE = carbapenem-resistant enterobacteriaceae, MRSA = methicillin-resistant *Staphylococcus aureus*			
** Multidrug-resistant pathogens included ESBLs, CRE, MRSA, and other MDR organisms			

Secondary outcome

The median (IQR) duration of MV was 22.0 (12.0, 34.0) days. The median duration of MV was significantly longer in LOVAP (23.0 (14.0, 35.5) VS 14.0 (10.0, 29.0); $p = 0.03$). The median (IQR) ICU LOS was 25.0 (15.0, 42.0) days. The median ICU LOS was significantly longer in LOVAP (26.5 (17.0, 43.0) VS 20.0 (11.0, 30.0); $p = 0.02$). The median hospital LOS was 34.0 (23.0,53.0). The median hospital LOS was significant longer in LOVAP (35.5 (24.0, 56.0) VS 26.5 (15.0, 44.0); $p = 0.01$). Tracheostomy was performed in 30.5% (38.1% of EOVAP and 28.4% of LOVAP). (Table 3). The hospital mortality during the study period was 31.1%. The hospital mortality was 16.7% in EOVAP and 35.1% in LOVAP that was significantly greater than EOVAP ($p = 0.02$). (Table 3)

Table 3
Outcomes of treatment in early-onset VAP (n = 42) and late-onset VAP (n = 148)

Outcomes	Early-onset VAP	Late-onset VAP	p-value
Median duration mechanical ventilator (day, IQR)	14.0 (10.0, 29.0)	23.0 (14.0, 35.5)	0.03*
Median ICU length of stay (day, IQR)	20.0 (11.0, 30.0)	26.5 (17.0, 43.0)	0.02*
Median hospital length of stay (day, IQR)	26.5 (15.0, 44.0)	35.5 (24.0, 56.0)	0.01*
Performed tracheostomy (n.%)	16.0 (38.1)	42.0 (28.4)	0.22
Hospital mortality (n,%)	7.0 (16.7)	52.0 (35.1)	0.02*
*p-value < 0.05			

Factor associated hospital mortality

Univariate and multivariate analysis were performed to assess factors associated with hospital mortality. On univariate analysis, the patients who were of an age ≥ 60 years (cOR = 2.19; 95% CI 1.11–4.33; p = 0.02), were admitted in the medical ICU (cOR = 2.28; 95% CI 1.20–4.29; p = 0.01), had a SAPII score ≥ 40 ICU (cOR = 2.49; 95% CI 1.28–4.86; p = 0.007), received improper empirical antibiotics (cOR = 2.27; 95% CI 1.10–4.68; p = 0.02), or were late-onset VAP (cOR = 2.71; 95% CI 1.12–6.52; p = 0.02) were statistically associated with hospital mortality of VAP patients. With stepwise backward multivariate analysis, having a SAPII score ≥ 40 was the only statistically significant factor associated with hospital mortality (aOR = 2.22; 95% CI 1.08–4.54; p = 0.02). (Table 4)

Table 4
Factors associated with hospital mortality in VAP patients.

Factors	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value*
Age ≥ 60 years	2.19 (1.11–4.33)	-	0.02*
Having underlying diseases	0.99 (0.47–2.08)	-	0.99
Patient at medical ICU	2.28 (1.20–4.29)	-	0.01*
Having SAPII score ≥ 40	2.49 (1.28–4.86)	2.22 (1.08–4.54)	0.02*
Resistant gram-negative organisms	1.04 (0.51–2.13)	-	0.92
Receiving improper empiric antibiotics	2.27 (1.10–4.68)	-	0.02
Late-onset VAP	2.71 (1.12–6.52)	-	0.02

OR = odds ratio; *p-value for 95% CI of adjusted OR

Discussion

The study revealed that the most common pathogens were a gram-negative organisms. *A. baumannii*, *K. pneumoniae*, *P. aeruginosa* were common pathogens in both groups while *S. maltophilia* was increased in late-onset VAP. The pathogens from this study did not differ between EOVAP and LOVAP. The results of this study were similar to other tertiary centers in Thailand[26, 27]. Of these, *A. baumannii*, *K. pneumoniae*, *P. aeruginosa* were the common pathogens of VAP. These studies, however, did not address the causative organisms into early-onset VAP and late-onset VAP. Three studies from different tertiary-care centers of India had results similar to the present study[13, 14, 28]. *A. baumannii*, *K. pneumonia* and *P. aeruginosa* were common pathogens in both EOVAP and LOVAP. The pathogens of EOVAP from this study differed from pathogens mentioned in the recent guideline[16]. The results supported that empiric treatments should be guided by a local distribution of pathogens that recognized and treatments are recommended by the Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia in 2016 by IDSA/ATS guideline[2].

Gram-positive bacteria were identified in only 2.6% and most of them were MRSA. The prevalence of drug-resistance gram-positive bacteria in this study was markedly lower as compared to the study of the pathogens of VAP in Thailand by Chittawatanarat et al, Inchai et al and Werarak et al[26, 27, 29]. Reechaipichitkul et al conducted a study of the causative organisms of VAP in the same center during 2008–2009. The study indicated MRSA was responsible for 6–7% of the total causative organisms[8]. The majority of S. *aureus* colonization in the respiratory tract are in the nares and throat. Chlorhexidine is a topical antiseptic, which is most active against gram-positive bacteria[30]. Our center has applied selective oral decontamination (SOD) with chlorhexidine since 2011. This might have reduced the incidence of VAP due to MRSA.

The purpose of differentiation of VAP into EOVAP and LOVAP was to guide empiric antibiotic treatment to cover MDR bacteria. Inappropriate and delayed empirical therapy is associated with higher mortality in VAP patients[31–33]. The study found that LOVAP had a significantly higher proportion of MDR pathogens than EOVAP ($p = 0.007$). The results endorsed the Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia in 2016 by IDSA/ATS suggested that VAP developed after 5 days of hospitalization had a greater risk of MDR pathogen presence than VAP developed earlier[2]. Therefore empiric broad-spectrum antibiotics against MDR were recommended for LOVAP.

Furthermore, this current study demonstrated that LOVAP had significantly longer MV days, ICU LOS, and hospital LOS than EOVAP. The hospital mortality was significantly greater in LOVAP (35.1% VS 16.7%, $p = 0.02$). These worse outcomes of LOVAP also observed by Khan et al[23]. The implementation of VAP prevention might reduced the cost of hospitalization and unnecessary mortality, especially in LOVAP[34].

The strengths of this study were that the recorded data were complete because VAP was under regular surveillance of our institute by infection control ward nurses (ICWNs) and confirmed by infection control unit.

This study had some limitations including 1) the small sample size, especially in EOVAP 2) the results of this study cannot be applied to VAP in immunocompromised patients, 3) this study was a single-center study, which had this limitation for application to various other hospitals; an empirical **treatment** for VAP should be guided by local pathogen distribution.

Conclusion

In conclusion, LOVAP was significantly higher MDR pathogen, MV days, ICU LOS, hospital LOS and hospital mortality than EOVAP. A broad-spectrum antibiotic to cover MDR pathogens should be considered in LOVAP. The factor associated with hospital mortality of VAP was a SAPII score ≥ 40.

Abbreviations

VAP

ventilator-associated pneumonia; ICU:intensive care unit; EOVAP; ealy-onset ventilator associated pneumonia; LOVAP:late-onset ventilator associated pneumonia; LOS:length of stay; MV:mechanical ventilator; MDR:multi-drug resistant; SAP II score:simplified acute physiology II score; INICC:International Nocosomial Infection Control Consortium; IDSA:Infectious Disease Society of America; ATS:American Thoracic Society; ERS:European Respiratory Society; ESICM:European Society of Intensive Care Medicine; ESCMID:European Society of Clinical Microbiology and Infectious Diseases; ALAT:Latin American Thoracic Association; IC:infectious control; ICWNs:infection control ward nurses; SOD:selective oral decontamination; MSSA:methicillin-sensitive *Staphylococcus aureus*; MRSA:methicillin-resistant

Staphylococcus aureus; ESBL:extended-spectrum beta-lactamase-producing; CRE:carbapenem-resistant enterobacteriaceae; CFU:colony forming unit; ml:millilitre; mg:milligram:SD:standard deviation; IQR:interquartile range; cOR:crude odds ratio; aOR; adjusted odds ratio; 95% CI:95% confidence interval

Declarations

Acknowledegements

The authors gratefully thank Professor James Arthur Will for editing the manuscript via the Faculty of Medicine Publication Clinic, KhonKaen University, Thailand. This study was supported by the Faculty of Medicine, KhonKaen University, Thailand

Author's contributions

P.V, A.S., W.R. developed the study design, statistical analysis, interpretation of data, manuscript preparation, and critical revision of intellectual content. W.C., I.A. conducted interpretation of data and manuscript preparation. The remaining authors reviewed of manuscript. All authors read and approved the final manuscript

Fundings

This research did not receive any fundings sources.

Availability of data and materials

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee, KhonKaen University (approval numberHE611281). There is no individual patient data is presented in the study, hence consent to publication is not applicable

Consents for publication

Not applicable

Competing interests

All authors have no completing interests.

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