# Outcomes and risk factors of ventilator-associated pneumonia in neonates

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Original article

***Background:*** **Ventilator-associated pneumonia (VAP) in neonates has been associated with high mortality and poor outcome. This study aimed to compare the incidence, risk factors, and outcomes of VAP and non-VAP conditions in neonates.**

***Methods:*** **We performed a prospective cohort study in a neonatal intensive care unit (NICU) in Thailand from January 2014 to December 2014. All neonatal patients who were ventilated more than 48 hours were enrolled.**

***Results:*** **There were 128 enrolled patients. The median (inter quartile range) gestational age and birthweight were 35 (30.2, 37.8) weeks and 2380 (1323.8, 3020.0) g. There were 17 VAP patients (19 episodes) and 111 non-VAP ones. The VAP rate was 13.3% or 10.1 per 1000 ventilator days. According to the multivariate analysis, a birthweight less than 750 g [adjusted odds ratio (aOR)=10.75, 95% confidence interval (CI)=2.35-49.16; *P*=0.002] and sedative medication use (aOR=4.00, 95% CI=1.23-12.50; *P*=0.021) were independent risk factors for VAP. Compared with the non-VAP group, the median difference in the VAP group yielded a significantly longer duration of NICU stay (18 days, *P*=0.001), total length of hospital stay (16 days, *P*=0.002) and higher hospital costs ($5113, *P*=0.001). The in-hospital mortality rate in the VAP and non-VAP groups was 17.6% and 15.3% (*P*=0.73), respectively.**

***Conclusions:*** **A neonatal birthweight less than 750 g and sedative medication use were independent risk factors for VAP. Our VAP patients experienced a longer duration of both NICU and hospital stay, and incurred higher hospitalization costs.**

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***Key words:*** **mechanical ventilation;**
**newborn;**
**risk factor;**
**sedatives;**
**ventilator-associated pneumonia**

## Introduction

Ventilator-associated pneumonia (VAP) is one of the most common device- and healthcare-associated infections in the critical care setting.[1] The exact rate of neonatal VAP is difficult to establish because the radiographic identification of pneumonia is difficult and diagnostic procedures commonly used in adults are rarely used in neonatal patients. The National Healthcare Safety Network reported that concerning the device-associated module, the pooled mean VAP rate for neonates was 1.1/1000 ventilator days.[2] In the International Nosocomial Infection Control Consortium report, 2004-2009 data summary of 36 countries, the pooled mean VAP rate among neonates was 9/1000 ventilator days.[3] Other investigators have reported rates varying from 4/1000 to 25.6/1000 ventilator days.[1,4-6] VAP is a cause of significantly increased morbidity and mortality rates, utilization of healthcare resources, and excess cost.[4,5,7,8]

The epidemiology, pathogenesis, risk factors and outcomes of VAP are well described in adults; however, few data exist regarding VAP in pediatric patients, especially for neonates. Recognized risk factors for VAP in pediatric patients include female gender, genetic syndrome, postsurgical admission diagnosis, presence of enteral feeds, use of narcotic medications, steroids, reintubation, bloodstream infection, prior antibiotic therapy, and bronchoscopy.[7,9] In addition, VAP in pediatrics has been associated with a prolonged duration of mechanical ventilation as well as an increased length of intensive care unit (ICU) stay, total median hospital costs, and absolute hospital mortality compared to those

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among patients without VAP.[7]

Because neonates have a different anatomy, physiology, and underlying diseases compared with adults and older children, specific studies are needed in the neonate population. A recent meta-analysis study of the risk factors for VAP in neonates reported that length of stay, mechanical ventilation, reintubation, enteral feeding, transfusion, low birth weight (BW), prematurity, and parenteral nutrition were independent risk factors for the development of VAP.[10]

Furthermore, there are a few published studies in mechanically-ventilated neonates describing the accurate VAP rate, risk factors and outcomes in Thailand, and a limited number of prospective studies concerning VAP have been performed in neonates. We performed a prospective cohort study of neonates who were admitted to the neonatal ICU (NICU), Songklanagarind Hospital, from January 1, 2014 to December 31, 2014. This study aimed to compare the incidence, risk factors, and outcomes of VAP and non-VAP conditions in neonate patients.

## Methods

### Setting

The NICU of Songklanagarind Hospital is a level III, 15-bed unit that is part of a university-affiliated teaching hospital at Prince of Songkla University, Songkhla, Thailand. It has approximately 450 admissions per year. The Songklanagarind Hospital NICU receives referrals from the whole southern region of Thailand.

### Patients

All inborn and outborn neonates who were admitted to the NICU of Songklanagarind Hospital, Songkhla, Thailand and born during the January 1, 2014-December 31, 2014 period were screened for study enrollment and were considered eligible if ventilated for more than 48 hours. Patients who were transferred to the NICU from an outside hospital were also included. The exclusion criteria were death within 48 hours of NICU admission, unobtainable consent and an identified genetic syndrome. This study was approved by the Ethics Committee of Faculty of Medicine, Prince of Songkla University.

### Data collection

Medical records comprising charts, daily flow sheets, laboratory and radiographic reports were collected prospectively by the investigators. The data collected involved demographics and potential risk factors (medications, catheter devices, invasive procedures, nutritional methods, ventilator use, length of stay in the NICU, concurrent healthcare-associated infections). Both the laboratory data concerning the culture result of the tracheal aspirate and the radiographic data were recorded. The radiographic findings were reviewed by a pediatric radiologist for patients who developed VAP in order to confirm the diagnosis of VAP and rule out other possible diagnoses. The pediatric radiologist reviewed the chest radiographs on the day of the diagnosis, 3 days prior to the diagnosis, and on days 2 and 7 after the diagnosis.

When determining whether to report multiple episodes of VAP in a single patient, we looked for evidence of resolution of the initial infection. For this purpose, the combination of new signs and symptoms and radiographic testing evidence was required. For patients with VAP, the risk factors were evaluated from the time of admission until the onset of VAP. For patients who did not develop VAP, the risk factors were evaluated for their entire NICU stay.

Regarding the collection of the endotracheal aspirate, these steps were followed. After proper hand washing and wearing sterile gloves before suctioning, the endotracheal secretions were collected by instilling 1-2 mL of sterile normal saline into the endotracheal tube and then collecting it back with the help of a sterile mucous trap. The specimen collected was transported to the laboratory within one hour of collection. Blood and sputum specimens had to be collected within 48 hours of each other.

### Definitions

Our criteria for the diagnosis of VAP followed the U.S. Centers for Disease Control and Prevention guidelines for infants <1 year old.[11] Therefore, the infant required mechanical ventilation more than two calendar days when all elements of the pneumonia criterion were first present together, with day of ventilator placement being day 1, and the ventilator was in place on the date of event or the day before. The pneumonia criterion needed to satisfy both the clinical and radiographic criteria. The clinical criteria were worsening gas exchange [e.g., $O_2$ desaturation (e.g., pulse oximetry <94%), increased oxygen requirements or increased ventilator demand] and at least three of the following: 1) temperature instability; 2) leukopenia [<4000 white blood cell (WBC)/$mm^3$] or leukocytosis (>15 000 WBC/$mm^3$) and a left shift (>10% band forms); 3) new onset of purulent sputum or change in sputum characteristics, or increased respiratory secretions or suctioning requirements; 4) apnea, tachypnea, nasal flaring with retraction of the chest wall or grunting; 5) wheezing, rales or rhonchi; 6) cough; 7) bradycardia (<100 beats/minute) or tachycardia (>170 beats/minute). Concerning the radiographic criteria, one of following had to be present: 1) a new or progressive pulmonary infiltration; 2) consolidation; 3) cavitation; 4) pneumatoceles. However, the patient with either respiratory distress syndrome, bronchopulmonary dysplasia or pulmonary edema

needed 2 or more serial X-rays showing one of the above elements of the radiographic criteria.

Intermittent positive-pressure ventilation, nasal positive end-expiratory pressure and continuous nasal positive airway pressure were not considered ventilators. For both the presence of a purulent sputum and change in the characteristics of the sputum, repeated notations over a 24-hour period were kept. Change in sputum characteristics referred to its color, consistency, odor and quantity. Tachypnea was defined as >75 breaths per minute in premature infants born between <37 and up to 40 weeks of gestation, and >60 breaths per minute in patients <1 month old.[11]

For VAP patients, the duration of ventilation was considered a risk factor and defined as the duration of endotracheal intubation until VAP diagnosis. For non-VAP patients, it was defined as the duration of endotracheal intubation until extubation. Administration of medications such as dexamethasone, total parenteral nutrition, intralipid administration, antihistamine type 2, and use of narcotic medications and/or inotropes were considered risk factors if the infant receiving any dose of medication more than 3 consecutive days before onset or during admission, for non-VAP infants, developed VAP. Invasive procedures (reintubation, umbilical arterial or venous catheterization, central venous catheterization, orogastric tube insertion) were considered risk factors if the procedure occurred before the onset of VAP. Congenital heart disease, persistent pulmonary hypertension of the newborn and patent ductus arteriosus were determined if the infant was diagnosed by echocardiography.

Respiratory distress syndrome was defined according to clinical and radiographic criteria. The clinical criteria were $PaO_2$<50 mmHg at room air, central cyanosis at room air, supplemental oxygen requirement to maintain $PaO_2$>50 mmHg or supplemental oxygen requirement to maintain a pulse oximeter saturation over 85% within the first 24 hours of life. The radiographic criteria were reticulogranular appearance in the lung fields with or without low lung volumes and air bronchograms within the first 24 hours of life.

The determination of meconium aspiration syndrome required the satisfaction of all of the following criteria: presence of meconium-stained amniotic fluid at birth; respiratory distress; $PaO_2$<50 mmHg at room air, central cyanosis at room air or supplemental oxygen requirement to maintain $PaO_2$>50 mmHg; abnormal chest X-ray compatible with the diagnosis of meconium aspiration (coarse irregular or nodular pulmonary densities, areas of diminished aeration or consolidation alternating with areas of hyperinflation and generalized hyperinflation); and absence of culture proving early-onset bacterial sepsis or pneumonia.

Retinopathy of prematurity (ROP) was diagnosed if an indirect ophthalmologic examination for ROP was performed at any time and yielded the required findings.[12]

Bronchopulmonary dysplasia was defined as a need for supplemental oxygen for at least 28 days. The times of point assessment were at 36 weeks' postmenstrual age for babies born before 32 weeks' gestational age or at 56 days of life for babies born at or beyond 32 weeks' gestational age or discharged home, whichever came first.[13]

In-hospital mortality was defined as a patient who died at any time during the entire course of hospitalization. The duration of NICU stay was defined as the duration of admission until discharge from NICU, whereas the total length of stay was defined as the duration of admission until discharge from Songklanagarind Hospital.

### Outcomes

The primary outcome was mortality between VAP and non-VAP patients. The secondary outcomes were length of hospital and NICU stay and hospital cost for VAP compared with non-VAP patients.

### Statistical analysis

The R program (R foundation for statistical computing, Vienna, Austria, 2014) and epicalc package (R package version 2.15.1.0, Songkhla, Thailand, 2012) were used to develop a database of categorical and continuous variables. Student's *t* test was used to compare continuous variables, and the Fisher exact test was used to compare categorical variables. The multivariate analysis was carried out using a stepwise logistic regression model for risk factor analysis. A *P* value of less than 0.05 indicated a statistical significance.

Regarding the multivariate analysis of risk factors associated with VAP, variables significantly associated with VAP on univariate analysis, $P$<0.2, and variables identified by previous studies as risk factors for VAP such as ranithidine use, reintubation, previous blood-stream infection, and blood transfusion were entered into the multivariate regression analysis.

## Results

During the study period, a total of 454 patients were admitted, 128 of them met the study criteria, and were consented and enrolled. There were 61 episodes of clinical VAP in 45 patients and 19 episodes of clinical and radiographic VAP in 17 patients (Fig.). One patient had 3 episodes of VAP and the other patient had only 1 episode. The total ventilator days were 1876; therefore, the overall incidence of VAP was 13.3% (17/128) or 10.1 per 1000 ventilator days. The population characteristics of the 128 patients were analyzed. The median [inter quartile

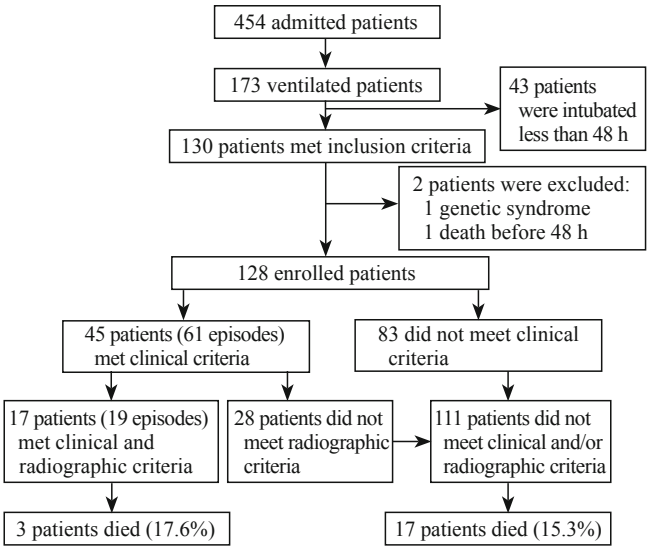


**Fig.** Participants enrolled in the study.

**Table 1.** Comparison of population characteristics between VAP and non-VAP groups

| Characteristics | VAP ($n$=17), $n$ (%) | Non-VAP ($n$=111), $n$ (%) | $P$ value |
|---|---|---|---|
| Gestational age, wk* | 33 (31, 37) | 35 (30, 38) | 0.61 |
| Premature infant | 10 (58.8) | 65 (59.1) | 0.81 |
| Birth weight, g* | 2325 (810, 3100) | 2400 (1380, 2982.5) | 0.51 |
| Birth weight, g | | | |
| <750 | 4 (23.5) | 5 (4.5) | 0.02 |
| <1000 | 5 (29.4) | 19 (17.1) | 0.06 |
| 751-1000 | 1 (5.9) | 14 (12.6) | 0.69 |
| 1001-1500 | 0 (0) | 15 (13.5) | 0.13 |
| 1501-2500 | 4 (23.5) | 24 (21.6) | 1.00 |
| >2500 | 8 (47.1) | 53 (47.7) | 0.84 |
| Male | 9 (52.9) | 65 (58.6) | 0.86 |
| Inborn | 13 (76.5) | 80 (72.1) | 1.00 |
| Apgar score at 1 min* | 6 (5, 8) | 8 (4, 9) | 0.47 |
| Apgar score at 5 min* | 8 (7, 9) | 9 (7, 9) | 0.95 |
| Maternal condition | | | |
| Antenatal steroid | 7 (41.2) | 41 (36.9) | 0.95 |
| Prolonged premature rupture of membrane | 0 (0) | 8 (7.2) | 0.60 |

VAP: ventilator-associated pneumonia. *: values are median (inter quartile range).

**Table 2.** Risk factor comparison between VAP and non-VAP groups

| Risk factors | VAP ($n$=19), $n$ (%) | Non-VAP ($n$=111), $n$ (%) | $P$ value |
|---|---|---|---|
| Duration of ventilation, d* | 6.0 (2.0, 7.5) | 7.0 (3.0, 12.0) | 0.07 |
| Underlying disease | | | |
| Respiratory distress syndrome | 9 (47.4) | 43 (38.7) | 0.65 |
| Congenital heart disease | 4 (21.1) | 23 (20.7) | 1.00 |
| Meconium aspiration syndrome | 2 (10.5) | 10 (9.0) | 0.69 |
| Persistent pulmonary hypertension of the newborn | 2 (10.5) | 6 (5.4) | 0.33 |
| Surgical case | 2 (10.5) | 15 (13.5) | 1.00 |
| Medication | | | |
| Dexamethasone | 3 (15.8) | 4 (3.6) | 0.06 |
| Surfactant | 3 (15.8) | 24 (21.6) | 0.76 |
| Parenteral alimentation | 16 (84.2) | 93 (83.8) | 1.00 |
| Sedative use | 9 (47.4) | 23 (20.7) | 0.02 |
| Inotrope | 15 (78.9) | 74 (66.7) | 0.43 |
| Antihistamine type 2 | 8 (42.1) | 22 (19.8) | 0.04 |
| Blood transfusion | 13 (68.4) | 73 (65.8) | 0.97 |
| Previous bloodstream infection | 1 (5.3) | 15 (13.5) | 0.47 |
| Invasive procedures | | | |
| Thoracocentesis | 3 (15.8) | 31 (27.9) | 0.40 |
| Reintubation | 10 (52.6) | 26 (23.4) | 0.02 |
| Umbilical artery catheter | 11 (57.9) | 74 (66.7) | 0.63 |
| Umbilical vein catheter | 17 (89.5) | 88 (79.3) | 0.53 |

VAP: ventilator-associated pneumonia. *: values are median (inter quartile range).

range (IQR)] gestational age and BW were 35 (30.2, 37.8) weeks and 2380 (1323.8, 3020.0) g, respectively. Fifty-eight percent (74/128) of the population was male, whereas 72.7% (93/128) were inborn patients. The median (IQR) Apgar scores were 7 (5, 9) and 9 (7, 9) at 1 and 5 minutes, respectively. The in-hospital mortality rate and crude case-fatality rate were 15.6% (20/128) and 17.6% (3/17). The median (IQR) duration of ventilation and length of stay were 8.0 (4.0, 18.0) and 26.0 (13.0, 42.5) days. The median (IQR) hospital cost was $5346.3 (2856.3, 9073.6) (1 USD≈32 THB).

The characteristics and risk factors of the VAP and non-VAP subjects are compared in Tables 1 and 2. On univariate analysis, compared with the non-VAP group, the VAP group had a significantly different less-than-750-g BW ($P$=0.02), history of sedative use ($P$=0.02), history of antihistamine use ($P$=0.04) and reintubation rate ($P$=0.02). The multivariate analysis of risk factors for VAP found that BW≤750 g [adjusted odds ratio (aOR)=10.75; 95% confidence interval (CI)=2.35-49.16; $P$=0.002] and sedative medication use (aOR=4.00, 95% CI=1.23-12.50; $P$=0.021) were independently associated with VAP.

The median (IQR) duration of ventilation use before and after VAP diagnosis in the VAP group were 11 (4.0, 42.5) and 15 (7.5, 21.5) days, whereas the median (IQR) duration of ventilator use in the non-VAP group was 7.0 (3.0, 12.0) days. Table 3 shows the VAP rate stratified by BW. Besides a worsening gas exchange, the other clinical-criteria findings were tachypnea (63.2%), nasal flaring with retraction of the chest wall (52.6%), increased and changed color of secretion (47.2%), fever (42.1%), wheezing/rales/rhonchi (21.1%), tachycardia (10.5%) and hypothermia (5.3%). Moreover, the percentage of diagnosed VAP cases with a presence of microorganisms in endotracheal cultures was 78.9% (15/19). One third of the positive microorganism findings concerned *Acinetobacter baumannii* (5); the other cases were *Stenotrophomonas maltophilia* (3), *Klebsiella pneumonia* and *Enterobactor cloacae* (2), and *Pseudomonas aeruginosa*, *Escherichia coli* and *Sphingobacterium* spp. (1).

The outcomes compared between the VAP and non-VAP groups are shown in Table 4. Compared with the

**Table 3.** Comparison of ventilator utilization and standardized infection ratios stratified by birthweight in 3 studies

| First author, year | Birthweight (g) | | | | | |
|---|---|---|---|---|---|---|
| | ≤750 | 751-1000 | 1001-1500 | 1501-2500 | >2500 | Overall |
| **VAP rates per 1000 ventilator-days (VAPs/ventilator days)** | | | | | | |
| NHSN, 2011[2] (NICU level III) | 1.8 (93/51 592) | 1.3 (34/26 635) | 1.1 (17/15 969) | 0.5 (7/13 569) | 0.3 (7/22 930) | 1.3 (158/120 126) |
| INICC, 2012[3] | 3.1 (4/1272) | 7.2 (51/7121) | 8.8 (48/5424) | 10.1 (70/6900) | 11.1 (77/6936) | 9.0 (250/27 653) |
| This study, 2014 | 10.8 (6/556) | 4.1 (1/241) | 0 | 15.0 (4/267) | 12.2 (8/654) | 10.1 (19/1876) |
| **Ventilator utilization ratio (number of ventilator days/number of patient days)** | | | | | | |
| NHSN, 2011[2] | 0.43 (51 592/118 886) | 0.26 (26 635/100 973) | 0.12 (15 969/134 822) | 0.08 (13 569/173 799) | 0.14 (22 930/158 888) | 0.17 (118 695/687 368) |
| INICC, 2012[3] | 0.47 (1272/2716) | 0.31 (7121/22 796) | 0.13 (5424/40 875) | 0.11 (6900/65 358) | 0.12 (6936/59 569) | 0.14 (27 653/191 314) |
| This study, 2014 | 0.54 (556/1037) | 0.32 (241/758) | 0.36 (158/442) | 0.30 (267/888) | 0.44 (654/1478) | 0.41 (1876/4603) |
| **Standardized infection ratio [SIR=(number of VAP in this study×1000)/(pooled mean VAP from standard paper×ventilator days in this study)]** | | | | | | |
| SIR compared to NHSN, 2011[2] | 6.0 | 3.2 | 0 | 30.0 | 40.8 | 7.8 |
| SIR compared to INICC, 2012[3] | 3.5 | 0.6 | 0 | 1.5 | 1.1 | 1.1 |

VAP: ventilator-associated pneumonia; NHSN: National Healthcare Safety Network; INICC: International Nosocomial Infection Control Consortium; NICU: neonatal intensive care unit.

**Table 4.** Outcomes in VAP and non-VAP groups

| Outcomes | VAP (*n*=17) | Non-VAP (*n*=111) | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|
| In-hospital mortality, *n* (%) | 3 (17.6) | 17 (15.3) | | 0.73 |
| Duration of NICU stay (d), median (IQR) | 32 (16.5, 59.0) | 14 (9.0, 22.5) | | 0.001 |
| Duration of NICU stay more than 14 d, *n* (%) | 14 (82.4) | 50 (45.0) | 5.69 (1.55-20.93) | 0.008 |
| Total hospital stay (d), median (IQR) | 39 (29.0, 80.0) | 23 (12.0, 37.5) | | 0.002 |
| Total hospital stay more than 14 d, *n* (%) | 16 (94.1) | 74 (66.7) | 8.00 (1.02-62.67) | 0.020 |
| Hospital costs (US$), median (IQR) | 9710 (6092.7, 16513.2) | 4597 (2640.7, 7701.8) | | 0.001 |
| Hospital costs more than 5000 US$, *n* (%) | 14 (82.4) | 53 (47.7) | 5.11 (1.39-18.77) | 0.009 |

VAP: ventilator-associated pneumonia; CI: confidence interval; NICU: neonatal intensive care unit; IQR: inter quartile range.

**Table 5.** Risk factors and outcomes of VAP among neonates in prospective cohort and retrospective studies

| First author, country, year | Risk factors | Outcomes | VAP rate |
|---|---|---|---|
| **Prospective cohort studies** | | | |
| Apisarnthanarak, USA, 2003[5] | Previous bloodstream infection, duration of intubation | LOS NICU, death | <28 wk, 6.5*<br>>28 wk, 4*<br>28.3% (19/67)† |
| Petdachai, Thailand, 2004[14] | Umbilical catheterization, respiratory distress syndrome, insertion of orogastric tube | Duration of ventilation and hospital LOS | 70.3*, 50% (85/170)† |
| Srinivasan, USA, 2009[7] | Female, post-surgery, enteral feeds, use of narcotic medications | Duration of ventilation, LOS NICU, mortality rate | NA |
| Tripathi, India, 2010[15] | VLBW, duration of MV | LOS NICU | 37.2*, 30.6% (30/98)† |
| Badr, Egypt, 2010[16] | Prematurity, LBW, duration of MV, enteral feeds, umbilical catheterization | NA | 57.1% (32/56)† |
| Afjeh, Iran, 2012[6] | Duration of MV, birth weight, purulent tracheal aspirate | NA | 11.6*, 17.3% (14/81)† |
| Cernada, Spain, 2014[17] | Duration of MV | Hospital LOS | 10.9*, 9.1% (18/198)† |
| Fallahi, Iran, 2014[18] | Lower gestational age and birth weight | Duration of ventilation, hospital LOS | 33.3% (22/66)† |
| Khattab, Egypt, 2014[19] | Prematurity, LBW, duration of MV, enteral feeds, umbilical catheterization | NA | 55.2% (47/85)† |
| Tan, not available, 2014[10] | LOS, duration of MV, reintubation, enteral feeds, transfusion, LBW, preterm, parenteral nutrition | NA | 8.1%-57.1%, 25.7% (370/1441)† |
| This study | Extremely LBW, sedative medication | Duration of MV, LOS NICU, hospital costs | 10.1*, 13.3% (17/128)† |
| **Retrospective studies** | | | |
| Yuan, China, 2007[20] | MV | LOS NICU, duration of MV, hospital costs | 20.1% (52/259)† |
| Deng, China, 2011[4] | BW, MV, parenteral alimentation, dexamethasone, respiratory disease | LOS NICU | 25.6*, 33.5% (117/349)† |
| Kawanishi, Japan, 2014[21] | Birthweight <626 g | NA | 9.0*, 15.5% (11/71)† |

LOS: length of stay; NICU: neonatal intensive care unit; MV: mechanical ventilator; LBW: low birth weight; VLBW: very low birth weight; NA: not available; VAP: ventilator associated pneumonia. *: VAP rate (episodes per 1000 ventilator days); †: proportion (number of patients with VAP/number of ventilated patients).

non-VAP group, the median difference in the VAP group yielded a significantly longer duration of NICU stay (18 days, *P*=0.001), total length of hospital stay (16 days, *P*=0.002) and higher hospital costs ($5113, *P*=0.001).

## Discussion

A very big difference in reported VAP rate can be observed among different studies, 4-70.3/1000 ventilator days, whereas the highest VAP incidence rate has been reported in Thailand.[14] This discrepancy in incidence may be explained by the different diagnostic criteria for VAP in each study and the time of study (Table 5). Neonates of a BW of less than 750 g must undergo endotracheal extubation as soon as possible in the sophisticated non-invasive ventilation era. The standardized infection ratios (SIRs) are similar to those in developing countries, except for infants with a BW of less than 750 g that are higher. Moreover, the SIRs for infants with a BW of more than 1500 g are much higher than those in developed countries (30-40 times) and the ventilator utilization ratio is higher (2.4-2.9 times) when compared with those of previous studies from both developed and developing countries (Table 3). Sedatives are given in cases of patient-ventilator dyssynchrony; however, they should be avoided if possible.

Our multivariate analysis of the risk factors revealed that only sedative medication use ($P$=0.02) and BW less than 750 g ($P$=0.002) were significant independent risk factors associated with the development of VAP. To our knowledge, no previous study in pediatric patients has found an association between sedative medication use and VAP. It is known that the use of sedative medications prolongs the exposure to risk factors for ICU-acquired infection and ICU stay among adults. A prolonged stay in the ICU has been reported to associate with an increased exposure to invasive procedures that were major risk factors for VAP.[22-24] Furthermore, unconscious patients are more likely to experience a microaspiration of contaminated oropharyngeal secretions, which are critical in the pathogenesis of VAP.[22] In addition to an increased exposure to invasive procedures and microaspiration, sedative medications have also been shown to alter cellular function and other mediators of the immune system, which possess a significant immunosuppressive effect.[25] Previous studies have shown that a low BW was associated with the development of VAP.[4,10,15,16,18,19,21] This study, however, found that a BW of less than 750 g was a significant independent risk factor associated with the development of VAP ($P$=0.004). Because patients with a BW of less than 750 g are extremely premature, their immune system is underdeveloped,[26,27] they are more likely to experience longer hospital stays, and an increased exposure to invasive procedures that may predispose them to the development of VAP.[28]

According to a meta-analysis, length of hospital stay, duration of mechanical ventilation, reintubation, enteral feeds, transfusion, preterm status, and parenteral nutrition are risk factors of VAP in neonates;[10] however, they were not found to be independently associated with VAP in our study. One study reports previous bloodstream infection to be a significant independent risk factor for VAP.[5] However, in none of our VAP-group patients, VAP was caused by the same organism responsible for their blood stream infection. Hence, in our cases, it is unlikely that VAP occurred as a direct consequence of blood stream infection. Moreover, it is well-known that VAP increases mortality rate.[4,5] In our study, there was no significant factor that may underpower the detection of mortality in VAP patients. However, VAP affects the duration of both NICU and hospital stay, and hospital costs, which, in our study, were significantly higher than those of patients without VAP. This finding was similar to those of previous studies.[4,7,14,20,29]

The organisms responsible for most VAP cases in the neonatal intensive care unit are gram-negative bacilli such as *Pseudomonas aeruginosa*, *Eschericha coli*, *Klebsiella pneumonia* and gram-positive cocci such as *Staphylococcus aureus*.[5,6,16] In Thailand, only one study has reported *Pseudomonas aeruginosa* to be the most common organism isolated in such cases.[14] *Acinetobacter baumannii* has emerged as one of the most troublesome pathogens for healthcare institutions, particularly in the intensive care unit, and has become the leading cause of VAP. A high mortality rate from this causative microorganism has been reported.[30,31]

The strengths of this study are: 1) this is a prospective cohort study showing the standardized infection and ventilator utilization ratios stratified by BW; 2) a pediatric radiologist confirmed all of the VAP diagnoses by reviewing chest X-rays in order to rule out other possible diagnoses. There are some limitations to this study: 1) it is difficult to identify pathogenic organisms or colonizations via tracheal aspiration because a bronchoalveolar lavage may not be safe for sick babies; however, research on the efficacy of BAL and non-BAL in the diagnosis of VAP among neonates remains scarce; 2) the small sample size, especially that of VAP patients, was an underpowering factor and should carefully interpret all of the results with the wide confidence interval.

In conclusion, a BW of less than 750 g and sedative use were identified as major risk factors associated with the development of VAP in neonates. Moreover, VAP patients had poor outcomes as well as prolonged durations of both NICU and hospital stays, and higher total hospital costs. Therefore, we recommend that both neonatologists and pediatricians avoid the unnecessary use of sedative medications in mechanically-ventilated patients.

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