Original Article

Surveillance of Ventilator-associated Pneumonia in a Neonatal Intensive Care Unit: Characteristics, Risk Factors, and Outcome

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Abstract

Background: This study determined the incidence, characteristics, risk factors, and outcomes of ventilator-associated pneumonia (VAP) in newborns hospitalized in a Neonatal Intensive Care Unit (NICU) in Tehran, Iran.

Methods: A prospective cohort study was carried out in the NICU of Mahdieh Hospital over a period of one year, from December 2008 to November 2009, on all neonates mechanically ventilated for more than 48 hours. VAP was diagnosed in accordance with the CDC definition of nosocomial pneumonias for patients younger than 12 months. Risk factors relevant to the development of VAP were studied. Multiple logistic and Cox regression analysis were performed to determine independent predictors for VAP and survival rate, respectively.

Results: There were 81 neonates enrolled. VAP occurred in 14(17.3%), at a rate of 11.6/1000 days on the ventilator. Gram negative bacteria were the predominant etiologic agents.The most common bacterial isolates from the endotracheal aspirate were *E.coli* (21.4%), *Klebsiella* (21.4%), and *Pseudomonas* (14.1%). The only VAP predictor was sputum [odds ratio (OR)=5.11, *P*=0.02]. Mortality rate for VAP was 2/14(14.3%). Duration of mechanical ventilation [hazard ratio (HR)=0.96, *P*=0.01], birth weight (HR=0.81, *P*<0.001), and purulent tracheal aspirate (HR=0.25, *P*<0.006) were independent predictors of overall survival.

Conclusion: VAP occurs at a significant rate in mechanically ventilated newborns. Additional studies are needed to accurately determine the incidence and risk factors in order to develop effective preventive and therapeutic protocols.

Keywords: Intensive care unit, neonate,rate, risk factors, ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is defined as nosocomial pneumonia in mechanically ventilated patients that develops more than 48 hours after initiation of mechanical ventilation.[1] VAP is the second most common nosocomial infection in neonates.It is associated with increased duration of hospital stay resulting in high morbidity and mortality among neonatal intensive care unit (NICU) patients,with an estimated incidence of 6% – 32%.[2–4]

VAP arises from aspiration of secretions,colonization of the areodigestive tract, the use of contaminated equipment, or medications.[5] Risk factors for VAP include prematurity, very low birth weight, severe underlying disease, prolonged duration of mechanical ventilation, use of wide spectrum antibiotics, prolonged hospital stay, inadequate pulmonary toilet, and extensive use of invasive devices and procedures.[4–6]

Understanding the microbiology of VAP is critical for choosing empirical antibiotic therapy. The most commonly isolated causative organisms are gram negative bacteria; however, gram positive bacteria have become increasingly more common over the past several years.[7–9]

The clinical criteria for diagnosis of VAP have been established by the National Nosocomial Infection Surveillance System (NNIS) and the Center for Disease Control and Prevention (CDC). However, it should be noted that no current gold standard exists for diagnosis of VAP in neonates.[1,4,10]

We performed this study to determine the rate, risk factors, causative agents, and outcome of VAP in neonates hospitalized in an NICU in Tehran, Iran. We found no published reports of studies that addressed VAP in neonates from Iran, although a few studies on VAP have been undertaken in older children and adults.[11,12]

Patients and Methods

This prospective study was carried out in an NICU at Mahdieh Hospital in Tehran, Iran, affiliated with Shahid Beheshti Medical University. The setting was a 40-bed NICU, managed by three experienced neonatologists with three neonatology fellows under training. The medical staff consisted of six pediatricians and two rotating pediatric residents. The nurse to patient ratio was 1:3 at all times during the day and night.

This study included all newborns who were given mechanical ventilation during a period of one year (December 2008 to November 2009). All relevant data that included detailed perinatal history, findings on physical examination, results of laboratory tests, imaging studies, and therapeutic approaches were meticulously recorded in the case notes and documented on a predesigned questionnaire.

Diagnosis of VAP was based on the criteria recommended by the CDC for infants less than one year of age,as follows: i) pneumonia that develops later than 48 hr after initiation of mechanical ventilation; ii) new or persistent infiltrations on chest X-ray; and iii) worsening gas exchange and at least three of the following criteria:

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Table 1. Characteristics of patients with and without VAP.

Descriptive variables	Infants with VAP (*n*=14)	Infants without VAP (*n*=67)
Males	9(64.3%)	47 (70.1%)
Gestational age (wks):	30 (range: 26–38)	31 (range :22–39)
<27	3 (21.4%)	15 (22.4%)
28–32	8 (57.1%)	34 (50.8%)
33–37	2 (14.3%)	10 (14.9%)
>37	1 (7.1%)	8 (11.9%)
Mean birth weight (g)	1654(830–2990)	1573 (560–3100)
<1500	9 (64.3%)	41 (61.2%)
1500–2500	2 (14.3%)	14 (20.9%)
>2500	3 (21.8%)	12 (17.9%)
Born in hospital	12 (85.7%)	50 (74.6%)
Surfactant therapy	10 (71.4%)	61 (91.0%)
Ranitidine therapy	5 (35.7%)	26 (38.8%)
Mean duration of hospitalization (days)	59±30	27±22
Mean duration of MV* (days)	39 (range: 5–86)	15 (range: 3–78)
*MV = mechanical ventilation		

Table 2. Laboratory and imaging tests in patients with and without VAP.

Para-clinical test	Patients with VAP No (%)	Patients without VAP No (%)
Positive CXR	14 (100)	7 (25.4)
Positive BAL	14 (100)	17 (25.4)
Purulent tracheal aspirate	11 (78.6)	28 (41.8)
Leukocytosis/leukopenia	14 (100)	48 (71.6)
Positive blood culture	0	6 (9)
Bacteria isolated on NB-BAL		
E.coli	3 (21.4)	3 (17.6)
Klebsiella	3 (21.4)	0
Pseudomonas	2 (14.3)	1 (5.9)
Acinobacter	1 (7.1)	1 (5.9)
Citrobacter	1 (7.1)	0
S. aureus	2 (14.3)	2 (11.8)
S. coagulasenegative	1 (7.1)	9 (52.9)
S. saprophyticus	1 (7.1)	1 (5.9)
S. = Staphylococcus		

temperature instability with no other recognized cause, new onset of purulent sputum, increase in respiratory secretions or increased need for suctioning, WBC < 4000/mm^3 or > 15000/mm^3, respiratory signs (apnea, tachypnea, nasal flaring, retraction, wheezing, rales, or ronchi), and bradycardia or tachycardia.[4]

Tracheal aspirate cultures for pathogenic bacteria were obtained and the results interpreted according to CDC recommendations for infants less than one year of age, which were the presence of positive cultures of pathogenic bacteria with counts >100000 CFU/mL from bronchial secretions obtained by non-bronchoscopicbroncho-alveolar lavage (NB-BAL) on the third and seventh days after initiation of mechanical ventilation. If the specimen was taken from the proximal part of the trachea or if the bacterial colonies on culture were < 100000 CFU/mL, the patient was excluded from the study. Specimens were also collected three days after onset of treatment to assess the response to therapy. All specimens were sent to the Pediatric Infectious Research Center affiliated with Shahid Beheshti University of Medical Sciences and were cultured by the Bactec method. Additional blood cultures, CBCs, blood chemistries, and arterial blood gases were obtained as needed.

Chest X-rays were taken on the first day, then once a week to check for new focal infiltrations until the infant was weaned off the ventilator and until complete resolution of symptoms. Additional chest X-rays were performed if required during the course of hospitalization. Chest X-rays were examined by a team comprised of two neonatologists and one experienced radiologist to differentiate VAP from other causes of lung involvement such as meconium aspiration and respiratory distress syndrome.

Figure 1 depicts the diagnostic algorithm for VAP used in the study group. During the course of hospitalization all alterations in the infant's symptoms, laboratory tests or ventilator settings were carefully documented.

Statistical analysis

Categorical data were summarized as percentage and quantitative data as mean ± standard deviation (SD). To evaluate each variable as a risk factor or protective factor for the development of VAP, logistic regression was performed. We used Cox regression analysis to identify variables that affected overall patient survival. For regression analysis, both beta coefficient and its exponential [odds ratio (OR) inlogistic regression and hazard ratio (HR) for Cox regression] were reported. *P*-values less than 0.05 were considered statistically significant and those between 0.05 and 0.10 as marginally significant.

Results

A total of 81 newborns with respiratory distress were enrolled in the study. Mean gestational age was 30 ± 4 weeks (range: 22 – 39 weeks). There were 72 (88.9%) preterm infants. The mean birth weight was 1587 ± 746 g (range: 560 – 3100g) and 50 (61.7%) weighed < 1500 g. Males comprised 69.1% of infants and 76.5% were singletons. Within six hours of birth, 45 (55.6%) neonates were intubated and started on mechanical ventilation. Table 1 demonstrates the characteristics of infants with and without VAP.

In 31 (38.3%) cases, NB-BAL cultures were positive and in 22 (71%), cultures grew clinically pathogenic microorganisms.As seen in Figure 1, the clinical and para-clinical findings in these 22 patients were as follows: worsening blood gases (i.e., hypoxemia, hypercarbia, and/or acidosis in all infants), positive chest

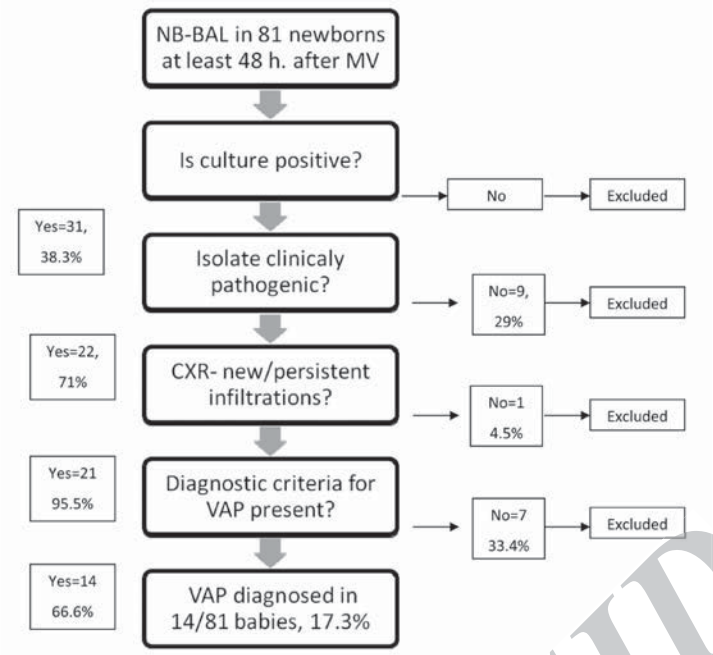

Figure 1. Diagnostic algorithm for VAP in the study group.

Table 3. Simple regression analysis of risk factors for VAP.

	B	OR	*P*-value
Gestational age (wks)			
<28	0.47	1.60	0.70
28–32	0.63	1.88	0.58
33–37	0.47	1.60	0.72
>37		Reference	
Gender			
Female	0.27	1.31	0.67
Male		Reference	
Birth weight (g)			
<1500	-0.13	0.88	0.86
1500–2500	-0.56	0.57	0.57
>2500		Reference	
Age MV* started	0.05	1.05	0.83
Surfactant dose	-0.64	0.53	0.13
Ranitidine therapy			
Yes	-0.13	0.88	0.83
No		Reference	
Dexamethasone treatment			
Yes	1.15	3.17	0.08
No		Reference	
Duration of MV	-0.004	1.0	0.84
Tracheal aspirate positive			
Yes	1.63	5.11	0.02
No		Reference	
Sputum			
Yes	1.63	5.11	0.02
No		Reference	

* Mechanical ventilation duration was calculated from date of application of MV until date of VAP diagnosis, otherwise until the baby was weaned off the ventilator.

X-rays(21), purulent secretions (11), respiratory distress (14), apnea (2), and leukocytosis (14). Based on specific criteria, we diagnosed VAP in 14 (17.3%) infants, which gave a prevalence of 11.6 cases of VAP/1000 ventilated patients. VAP was diagnosed after the infant had been on a ventilator for a period of 3 – 39 days (mean: 14±12 days).

Gram negative bacilli grew in 71.6% of culture positive secretions collected through NB-BAL. *E.coli* and *Klebsiella*each comprised 21.4% of the isolates. Blood cultures were negative in all infants diagnosed with VAP. Para-clinical findings in all patients are shown in Table 2.

No significant differences were noted in terms of gestational age, sex, and birth weight between infants with and without VAP (Table 3).

On multiple regression analysis, purulent sputum was identified as a risk factor for the development of VAP (OR=5.11, *P*=0.02).

Mortality

Two newborns with VAP and 24 without VAP died in the hospital.The proportional hazard (Cox regression analysis) identified the following factors (Table 4) as significant for overall survival in ventilated neonates: duration of mechanical ventilation, low birth weight, and profuse trachea-bronchial secretions (sputum).

Discussion

A widely differing incidence of VAP (6% – 32%) has been reported in various studies.[1–4] In a study by Apisarnthanarakin the

Table 4. Multiple regression analysis of risk factors for mortality.

	B	Hazard ratio	*P*-value
Duration of IMV*	-0.04	0.96	0.01
Birth weight (×100g)	-0.21	0.81	<0.001
Purulent tracheal aspirate	-1.39	0.25	0.006
*intermitant mechanical ventilation			

US, the author reported the incidence of VAP at 28.3% or 6.5 cases/1000 days of mechanical ventilation in preterm neonates with gestational ages < 28 weeks.[2] A report from Thailand has quoted the incidence of VAP at 50% (70.3 cases/1000 days on the ventilator).[3] Figures from other countries are as follows: China (20.1%), India (30.6%), and Egypt (57.1%).[7–9] In contrast, our results of 17.3% or 9 cases/1000 days on the ventilator are lower than most studies.

In our study VAP occurred 3 – 39 days after mechanical ventilation was started, the average being about two weeks. This finding was similar to the study by Tripathi from India.[8]

We identified only two variables as independent risk factors for the development of VAP: prolonged duration of mechanical ventilation (> 2 weeks) and antacid therapy. However, in contrast to some studies, birth weight < 1500 g, gestational age < 28 weeks, and sex were not related to the occurrence of VAP.

Apisarnthanarak, Yuan, Tripathi, and Mohamed have all reported prolonged ventilation to be a risk factor for VAP. Additional risk factors identified by these researchers included systemic infection,[2] repeated tracheal intubation and opiod therapy,[7] low birth weight,[8,9] and prematurity.[9] Low birth weight has not been quoted as an independent risk factor for VAP in other studies, although it may be associated with prolonged ventilation.[4,13,14]

Systemic infection or sepsis has been reported as a risk factor for VAP in one study, however, in that study microorganisms recovered from tracheal aspirates differed from those obtained from blood cultures.[2] None of the studies have reported a relationship between sepsis and VAP. According to most researchers, although systemic infection may worsen the course of VAP it does not play a role in its etiology.[2,4]

The association of antacid therapy with VAP, as seen in our study and in a study by Cook, can be explained by the fact that administration of antacids results in elevations in the stomach's pH, therefore increasing colonization with pathogenic bacteria in close proximity to the respiratory tract.[15]

As with other studies, gram negative bacteria (*E.coli, Klebsiella, and Pseudomonas*) were the most common agents that caused VAP in our patients.[2–4,7,9]

Duration of hospitalization and mechanical ventilation in our patients with VAP was significantly longer than those without VAP (Table 1).This was also seen in other studies, which emphasized the increasing morbidity caused by the development of VAP.[2,8,9]

In our patients with VAP, the mortality rate was not higher than other newborns in the NICU. Although low-birth weight was accompanied by increased mortality rate,the increased duration of mechanical ventilation was inversely related to mortality.Extremely ill neonates possibly die sooner and would not be ventilated for long periods of time. These findings are similar to studies conducted by Petdachai and Almuneef.[3,16] In a report by Apisranthanarak, VAP, and arterial catheterization have been associated with increased mortality.[2] In research conducted by Hemming, low birth weight, duration of ventilation, and virulent pathogens were recognized as risk factors for mortality.[13]

Limitations of the study

Since the CDC criteria for diagnosis of VAP applies to all infants < 1 year of age it may not be valid for newborns of very low birth weight (< 1000g), as Hyalin membrane disease (HMD), Chronic lung disease(CLD), sepsis, and Necrotizing enterocolitis (NEC) may be confused with VAP. We have attempted to minimize these errors through repeated examinations of chest X-rays and abdominal radiographs, and by performing blood cultures with the Bactecmethod to rule out NEC and sepsis.

VAP is an important cause of morbidity and occurs at a significant rate in neonates on mechanical ventilation. There is a need for larger studies to accurately define the incidence of VAP and to develop effective preventive and therapeutic protocols.

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