VENTILATOR-ASSOCIATED PNEUMONIA IN A NEWBORN INTENSIVE CARE UNIT

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Abstract. A prospective observational study was conducted in a neonatal intensive care unit to identify factors associated with the development of ventilator-associated pneumonia (VAP) in 170 infants aged less than 30 days who required mechanical ventilation for longer than 48 hours. VAP occurred in 85 infants (50 cases per 100 mechanically-ventilated infants) or 70.3 cases per 1,000 ventilator days. Stepwise logistic regression analysis identified 3 factors independently associated with VAP: umbilical catheterization [adjusted odds ratio (AOR)=2.5; 95% confidence interval (CI)=1.3 to 4.7; p=0.007]; respiratory distress syndrome (AOR=2.0; 95% CI=1.0 to 3.9; p=0.03); and insertion of orogastric tube (AOR=3.0; 95% CI=1.3 to 7.2; p=0.01). Infants with VAP had longer duration on ventilator (14.2 days *vs* 5.9 days; p<0.001) and longer hospital stay (28.2 days *vs* 13.8 days; p<0.001). Organisms were isolated in 42 specimens (49.4%) from endotracheal aspirate culture and in 17 specimens (20.0%) from hemoculture; *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter* spp were predominant. Polymicrobial infection was found in 11 specimens (12.9%) from endotracheal aspirate culture. Leukocytosis and blood gas values could not predict the presence of VAP. The mortality of infants with VAP (29.4%) did not differ significantly from that of infants without VAP (30.6%) (p=0.87). Certain clinical interventions might potentially affect the incidence of VAP and outcome associated with VAP.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a potentially lethal and common problem among mechanically-ventilated patients in intensive care units. In addition to its high mortality rate compared to other nosocomial infections, VAP is associated with prolonged hospitalization and considerable medical costs (Vincent *et al*, 1995; Fagon *et al*, 1996; Papazian *et al*, 1996; Bowton *et al*, 1999; Chastre and Fagon, 2002). Many factors predispose to acquiring VAP; infants mechanically ventilated in the neonatal intensive care unit (NICU) are at a particularly high risk of developing VAP because of poor host factors, severe underlying diseases, prolonged use of mechanical ventilation, inadequate pulmonary toilet and extensive use of invasive devices and procedures; gram-negative and gram-positive bacteria are the most common causative organisms (Goldman *et al*, 1983; Craven *et al*,1990; Cook *et al*, 1998; Grohskopf *et al*, 2002). Little data are available on VAP in the NICU and no exact number for infection rates is available (Stover *et al*, 2001).

The objective is to find the incidence of VAP and identify factors associated with the development of VAP and its outcome in a newborn intensive care unit.

MATERIALS AND METHODS

A prospective observational study was conducted in the newborn intensive care unit of Prachomklao Hospital, Petchaburi, Thailand, between August 1994 and August 2001. Infants aged less than 30 days who required mechanical ventilation for longer than 48 hours were evaluated. Those with pneumonia, severe birth asphyxia or congenital anomalies were excluded from analysis. The diagnostic criteria for VAP were modified from the CDC's definition for nosocomial pneumonia for patients younger than 12 months (Garner *et al*, 1988). Chest radiography was performed when VAP was suspected, if production of respiratory secretions increased, new onset of purulent tracheal sputum, or change in character of sputum was present. If the radiograph showed new or progressive infiltrate, cavitation, consolidation, or pleural effusion, then endotracheal aspirate culture and hemoculture were performed. With endotracheal aspirate, the catheter was blindly wedged into a distal bronchus and aspi-

rated secretions were recovered. No fluid was instilled during any of the procedures. Qualitative cultures were performed. The main outcomes measured were VAP and mortality. The study was approved by the Hospital Review Board.

Statistical analyses were conducted with STATA version 7.0. The influence of multiple risk factors was assessed by performing linear regression analysis on clinical settings and interventions to compare infants with and without VAP. Differences were considered significant when a p-value <0.05 was obtained.

RESULTS

Baseline characteristics of the infants

A total of 170 infants was entered into the study. The admissions were mainly due to prematurity, respiratory distress syndrome, and birth asphyxia. Most were admitted on the first day of life. Baseline demographic information on infants who developed VAP, and those without, showed no difference in sex, gestational age, birth asphyxia, hypoglycemia, hyperbilirubinemia, or prematurity (Table 1).

Table 1
Baseline demographic information of infants with and without VAP.

Variable	VAP (N=85)	Non-VAP (N=85)	p-value
Male	57	58	0.77
Gestational age (wk)	33.8	35.1	0.07
Birth asphyxia	35	34	0.71
Hypoglycemia	15	12	0.81
Hyperbilirubinemia	55	41	0.14
Prematurity	61	53	0.60

Rates of VAP

VAP occurred in 85 infants, a rate of 50 cases per 100 mechanically-ventilated infants, or 70.3 cases per 1,000 ventilator days. The mean duration of mechanical ventilation prior to the diagnosis of VAP was 9 days (range 2-36 days).

The mean birth weight of infants with VAP was significantly lower than that of infants without VAP (1,898 *vs* 2,214 g; p=0.01). Eighty percent of infants who got VAP weighed less than 2,500 g (Table 2). Infants with VAP had longer duration on ventilator (14.2 days *vs* 5.9 days; p<0.001) and longer hospital stay (28.2 days *vs* 13.8 days; p<0.001).

Factors associated with VAP

Significant clinical parameters, *ie* sex, birth asphyxia, hypoglycemia, hyperbilirubinemia, prematurity, umbilical catheterization, respiratory distress syndrome, insertion of orogastric tube, hematocrit, leukocyte count, percentage of neutrophils, pH, pCO_2, pO_2, were assessed (Table 3). Stepwise logistic regression analysis identified 3 factors to be independently associated with VAP: umbilical catheterization [adjusted odds ratio (AOR)=2.5; 95% CI=1.3 to 4.7; p=0.007]; respiratory distress syndrome (AOR=2.0; 95% CI=1.0 to 3.9; p=0.03); and insertion of orogastric tube (AOR=3.0; 95% CI=1.3 to 7.2; p=0.01).

Table 2
Clinical outcomes of infants with and without VAP.

Variable		VAP	Non-VAP	p-value
Mean birth weight (g)		1,898	2,214	0.01
<1,500 g	N(%)	34 (40.0)	22 (25.9)	0.05
1,501-2,500 g	N(%)	34 (40.0)	34 (40.0)	1.00
>2,500 g	N(%)	17 (20.0)	29 (34.1)	0.04
Duration of mechanical ventilation (day)		14.2	5.9	<0.001
Hospital stay (day)		28.2	13.8	<0.001
Mortality rate (%)		29.4	30.6	0.87
<1,500 g	N(%)	16 (64.0)	7 (26.9)	0.26
1,501-2,500 g	N(%)	5 (20.0)	9 (34.6)	0.23
>2,500 g	N(%)	4 (16.0)	10 (38.5)	0.44

Table 3
Adjusted odds ratio on clinical parameters

Parameter	Adjusted odds ratio	95% CI	p-value
Sex	0.9	0.4-1.8	0.77
Birth asphyxia	1.1	0.6-2.3	0.71
Hypoglycemia	1.1	0.4-2.8	0.81
Hyperbilirubinemia	1.7	0.8-3.4	0.14
Prematurity	0.8	0.4-1.8	0.60
Umbilical catheterization	2.5	1.3-4.7	0.007
Respiratory distress syndrome	2.0	1.0-3.9	0.03
Orogastric tube	3.0	1.3-7.2	0.01
Hematocrit	1.0	0.9-1.0	0.78
Leukocyte count	1.0	0.9-1.0	0.73
Percentage of neutrophils	0.9	0.9-1.0	0.33
pH	0.3	0.0-5.0	0.66
pCO_2	0.9	0.9-1.0	0.95
pO_2	0.9	0.9-1.0	0.17

Table 4
Organisms from endotracheal aspirate culture and hemoculture.

Organism	Endotracheal aspirate N=42 (%)	Hemoculture N=17 (%)
Pseudomonas aeruginosa	21 (38.2)	1 (5.9)
Klebsiella pneumoniae	15 (27.3)	3 (17.6)
Acinetobacter spp	14 (25.4)	7 (41.2)
Enterobacter spp	3 (5.5)	4 (23.5)
Coagulase-negative staphylococcus	2 (3.6)	2 (11.8)
Polymicrobials	11 (12.9)	-

Hematocrit, leukocytosis, percentage of neutrophils, and blood gas values (pH, pCO_2, pO_2) did not differ in the two groups.

Distribution of pathogens

Gram-negative organisms were the major cause of VAP in this study. Microorganisms were isolated in 42 specimens (49.4%) from endotracheal aspirate culture, where *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter* spp were predominant, and in 17 specimens (20.0%) from hemoculture, where *Acinetobacter* spp, *Enterobacter* spp and *Klebsiella pneumoniae* were predominant (Table 4). Polymicrobial infection was found in 11 specimens (12.9%) from endotracheal aspirate culture. Coagulase-negative staphylococcus was the only gram-positive organism that accounted for the etiology of VAP. Most of the bacterial isolates had significant antimicrobial resistance.

Complications

There were significant complications in infants with and without VAP (Table 5).

Infant mortality

Twenty-five infants with VAP and 26 infants without VAP died. The mortality of infants with VAP (29.4%) did not differ significantly from that of infants without VAP (30.6%) (p=0.87) (Table 2). The mortality rate increased in infants with a birth weight less than 1,500 g. Among infants who died, those with VAP had longer duration on a ventilator (13.1 *vs* 4.0 days; p<0.001). Organisms were

Table 5
Complications of infants with and without VAP.

Complication	VAP (N=85)	Non-VAP (N=85)
Pneumothorax	0	5 (5.9%)
Intraventricular hemorrhage	0	1 (1.2%)
Gastrointestinal bleeding	0	1 (1.2%)
Pulmonary hemorrhage	1 (1.2%)	0
Convulsion	3 (3.5%)	0
Necrotizing enterocolitis	1 (1.2%)	2 (2.4%)
Apnea	2 (2.4%)	1 (1.2%)

Table 6
Organisms causing mortality.

Organism	Numbers (%)
Pseudomonas aeruginosa	3 (33.3)
Klebsiella pneumoniae	2 (22.2)
Acinetobacter spp	2 (22.2)
Enterobacter spp	2 (22.2)

recovered from 9 infants, of which *Pseudomonas aeruginosa* accounted for 33.3% of deaths (Table 6).

DISCUSSION

Few data are available on VAP rates in the NICU and reported rates vary for each study, Stover *et al* (2001) reported an overall rate of 0.9 per 1,000 ventilator days in infants of weight more than 2,500 g, to 3.5 per 1,000 in those of weight less than 1,000 g. Cordero *et al* (2002) found an overall rate of 18.9% among low birthweight infants. There was a strong correlation between VAP and duration of ventilator use (Gaynes *et al*, 1991; Drews *et al*, 1995). Other potential risk factors for VAP have been examined in several large studies; the results have differed between study populations (Craven *et al*, 1990; Cook *et al*, 1998; Elward *et al*, 2002).

Clinical interventions for monitoring and therapeutic purposes can increase infants' risk of VAP. Placement of the enteral tube might enhance nasopharyngeal and gastric colonization with gram-negative bacilli that could be aspirated into the lower airway, initiating VAP (Atherton and white, 1978; Penn *et al*, 1981; Pingleton *et al*, 1986), while umbilical catheterization induced colonization as well as bloodstream dissemination of organisms (Drews *et al*, 1995; Gaynes *et al*, 1996; Stover *et al*, 2001). Infants with respiratory distress syndrome underwent prolonged use of mechanical ventilatory support, which potentiated exposure to contaminated respiratory equipment and contact with comtaminated or colonized hands of healthcare workers in the NICU (Craven *et al*, 1986).

There was a limitation in the sampling procedures used to obtain microbiologic specimens from the small respiratory tract in our study, in that invasive techniques to distinguish infection from colonization are not practical or feasible and may be harmful in small infants. They can impair blood-gas exchange, delay treatment, and lead to sepsis. The role of the protected-specimen brush (PSB) or bronchoalveolar lavage (BAL) in devising a therapeutic strategy superior to one based only on clinical evaluation has not been evaluated in infants (Chastre *et al*, 1994; Niedermann *et al*, 1994; Sanchez-Nieto *et al*, 1998). Percutaneous transthoracic aspiration is a definitive diagnostic procedure but is not commonly performed (Dorca *et al*, 1995). Endotracheal aspirate is the simplest means of obtaining respiratory secretions from infants receiving mechanical ventilation. Further study is needed to focus on practical issues to develop more reliable and less invasive diagnostic techniques and tools, and to search for safer and more cost-effective procedures in newborn infants (Papazian *et al*, 1995).

Gram-negative bacilli comprised nearly the whole isolates from cultures of specimens obtained from endotracheal aspirate and blood. Aerobic gram-negative bacilli are implicated in a wide spectrum of nosocomial infections in the ICU. Their emergence as significant pathogens seems to be related partly to the widespread use of broad-spectrum antibiotics, and partly to their ability to develop resistance rapidly to the major groups of antibiotics (Johanson *et al*, 1969; Schaberg *et al*, 1991; Trouillet *et al*, 1998; Waterer *et al*, 2001). Coagulase-negative staphylo-

coccus was the only gram-positive organism that accounted for the etiology of VAP and was associated with umbilical or central intravenous catheters (Freeman *et al*, 1990; Gaynes *et al*, 1996; Avila-Figueroa *et al*, 1998). Multiresistant strains of *Acinetobacter, Klebsiella* and *Pseudomonas* are difficult to treat and are implicated in a wide spectrum of nosocomial infections, predominantly in the ICU (Bergogne-Berezin, 1995; Towner, 1997).

VAP was the most common nosocomial infection contributing to death (Fagon *et al*, 1993; 1996). Mortality depended on birthweight, duration on ventilator and virulence of pathogen; those with lower birthweight and longer duration on ventilator were at higher risk (Hemming *et al*, 1976; Goldman *et al*, 1983). VAP caused by *Pseudomonas aeruginosa* had a higher rate of mortality (Taylor *et al*, 1995; Cunha, 2001). Fagon *et al* (1996) suggesting that in addition to the severity of underlying medical conditions and nosocomial bacteremia, VAP independently contributes to ICU patient mortality.

Since some clinical interventions increase the development of VAP, clinical guidelines for the treatment of VAP should be developed (Ibrahim *et al*, 2001), pediatricians should understand its epidemiology and participate in control measures, by reducing the risk of cross-contamination during mechanical ventilation, preventing colonization and aspiration, and caring for enteral tubes and umbilical catheters in sick infants.

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REFERENCES

Atherton ST, White DJ. Stomach as source of bacteria colonizing respiratory tract during artificial ventilation. *Lancet* 1978; 2: 968-9.

Avila-Figueroa C, Goldman DA, Richardson DK, Gray JE, Ferrari AF, Freeman J. Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns. *Pediatr Infec Dis J* 1998; 17: 10-7.

Bergogne-Berezin E. The increasing significance of outbreaks of *Acinetobacter* spp: the need for control and new agents. *J Hosp Infect* 1995; 30 (suppl): 441-52.

Bowton DL. Nosocomial pneumonia in the ICU-year 2000 and beyond. *Chest* 1999; 115 (3 suppl): 28S-33S.

Chastre J, Fagon J. Invasive diagnostic testing should be routinely used to manage ventilated patients with suspected pneumonia. *Am J Respir Crit Care Med* 1994; 150: 570-4.

Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165: 867-903.

Cook DJ, Walter SD, Cook RJ, *et al*. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998; 129: 433-40.

Cordero L, Ayers LW, Miller RR, Seguin JH, Coley BD. Surveillance of ventilator-associated pneumonia in very-low-birth-weight infants. *Am J Infect Control* 2002; 30: 32-9.

Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986; 133: 792-6.

Craven DE, Barber TW, Steger KA, *et al*. Nosocomial pneumonia in the 1990s: update of epidemiology and risk factors. *Semin Respir Infect* 1990; 5: 157-72.

Cunha BA. Nosocomial pneumonia: diagnostic and therapeutic considerations. *Med Clin North Am* 2001; 85: 79-114.

Dorca J, Manresa F, Esteban L, *et al*. Efficacy, safety, and therapeutic relevance of transthoracic aspiration with ultrathin needle in nonventilated nosocomial pneumonia. *Am J Respir Crit Care Med* 1995; 151: 1491-6.

Drews MB, Ludwig AC, Leititis JU, Daschner FD. Low birth weight and nosocomial infection of neonates in a neonatal intensive care unit. *J Hosp Infect* 1995; 30: 65-72.

Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. *Pediatrics*

2002; 109: 758-64.

Fagon J, Chastre J, Hance A, *et al*. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94: 281-8.

Fagon JY, Chastre J, Vaugnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 1996; 275: 866-9.

Freeman J, Platt R, Epstein MF, Smith NE, Sidebottom DG, Goldmann DA. Birth weight and length of stay as determinants of nosocomial coagulase-negative staphylococcal bacteremia in neonatal intensive care unit populations: potential for confounding. *Am J Epidemiol* 1990; 132: 1130-40.

Garner JS, Jarvis WT, Emori TG, *et al*. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16: 128-40.

Gaynes RP, Martone WJ, Culver DH, *et al*. Comparison of rates of nosocomial infections in neonatal intensive care units in the United States. National Nosocomial Infections Surveillance System. *Am J Med* 1991; 16: 192S-6S.

Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. *Pediatrics* 1996; 98: 357-61.

Goldman DA, Freeman J, Durbin WA. Nosocomial infection and death in a neonatal intensive care unit. *J Infect Dis* 1983; 147: 635-41.

Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, *et al*. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. *J Pediatr* 2002; 140: 432-8.

Hemming VG, Overall JC, Britt MR. Nosocomial infection in a newborn intensive care unit. *N Engl J Med* 1976; 294: 1310-6.

Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001; 29: 1109-15.

Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients: emergence of gram-negative bacilli. *N Engl J Med* 1969; 281: 1137-40.

Niedermann M, Torres A, Summer W. Invasive diagnostic testing is not needed routinely to manage suspect ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1994; 150: 565-9.

Papazian L, Thomas P, Garbe L, *et al*. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1995; 152: 1982-91.

Papazian L, Bregenon F, Thirion X, *et al*. Effect of ventilator-associated pneumonia on mortality and morbidity. *Am J Respir Crit Care Med* 1996; 154: 91-7.

Penn RG, Sanders WE, Sanders CC. Colonization of the oropharynx with gram-negative bacilli: a major antecedent to nosocomial pneumonia. *Am J Infect Control* 1981; 9: 25-34.

Pingleton SK, Hinthorn DR, Liu C. Enteral nutrition in patients receiving mechanical ventilation: multiple sources of tracheal colonization include the stomach. *Am J Med* 1986; 80: 827-32.

Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, *et al*. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. *Am J Respir Crit Care Med* 1998; 157: 371-6.

Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. *Am J Med* 1991; 91 (suppl 3B): S72-5.

Stover BH, Shulman ST, Bratcher DF, Brady MT, Levine GL, Jarvis WR. Nosocomial infection rates in US children's hospitals' neonatal and pediatric intensive care units. *Am J Infect Control* 2001; 29: 152-7.

Taylor GD, Buchanan-Chell M, Kirkland T, McKenzie M, Wiens R. Bacteremic nosocomial pneumonia. A 7-year experience in one institution. *Chest* 1995; 108: 786-8.

Towner KJ. Clinical importance and antibiotic resistance of *Acinetobacter* spp. *J Med Microbiol* 1997; 46: 721-46.

Trouillet JL, Chastre J, Vuagnat A, *et al*. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med* 1998; 157: 531-9.

Vincent JL, Bihari DJ, Suter PM, *et al*. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection Care (EPIC) study. *JAMA* 1995; 274: 639-44.

Waterer GW, Wunderink RG. Increasing threat of gram-negative bacteria. *Crit Care Med* 2001; 29 (suppl): N75-81.