Risk Factors for the Development of Ventilator – Associated Pneumonia in Critically-Ill Neonates

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Abstract: Ventilator-associated pneumonia (VAP), viewed as an inevitable consequence of critical illness, is increasingly accepted as an avoidable adverse health care incident. Whereas morbidity and mortality from VAP is well-documented in adults, it is poorly studied in children.This investigation was conducted to determine characteristics and possible risk factors for VAP, in critically ill neonates admitted to the neonatal intensive care unit (NICU). According to clinical pulmonary infection score (CPIS), 33 neonates were selected as having VAP and 24 neonates who did not develop VAP were assigned as non-VAP group. All neonates were subjected to case history, clinical examination, ABG, chest X-ray, and laboratory investigations (CBC, serum albumin, serum CRP, and blood culture). Neonates with VAP were subjected to broncheo-alveolar lavage (BAL) sampling. The BAL samples were subjected to macroscopic and microscopic examination, as well as quantitative cultures. Obtained results revealed that indications for mechanical ventilation (MV) included respiratory distress syndrome (RDS), congenital pneumonia, meconium aspiration syndrome (MAS), and hypoxic ischemic encephalopathy (HIE), with nonsignificant differences between VAP group and non-VAP group. VAP rates were significantly increased with decreased body weight and gestational age and with increased duration of NICU admission, duration of MV and use of invasive maneuvers. VAP was significantly associated with hypothermia, mucopurulent endotracheal tube (ETT) secretions, and radiological findings. The use of inotrops and corticosteroids was significantly noted among neonates with VAP than that among non-VAP neonates. Raised serum C-reactive protein (CRP), hypoalbuminemia and positive blood cultures were significantly associated with increased VAP rates. Cultures of BAL samples revealed *Klebsiella pneumoniae* (in 33%), *Pseudomonas aeruginosa* (in 21%), *Staphylococcus aureus* (in 15%), *Escherichia coli* (in 15%), *Pneumococci* (in 6%) and *Candida albicans* (in 9%). There was nonsignificant similarity in the type of organisms cultivated from either blood or BAL. In conclusion risk factors for the development of VAP include; 1) decreased body weight and gestational age, 2) increased duration of NICU admission, MV, and use of invasive maneuvers, 3) hypothermia, mucopurulent ETT secretions and the use of inotrops/ corticosteroids, 4) raised serum CRP, hypoalbuminemia and positive blood cultures and 5) nosocomial infection by *Klebsiella*, *Pseudomonas*, *Staph aureus*, *E coli* and *Candida*.
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1. Introduction

Nosocomial infections are a major cause of patient illness and death (Chen et al., 2005). Device-associated infections, such as catheter-associated urinary tract infections, and ventilator-associated pneumonia (VAP) pose the greatest threat to patient safety in intensive care units (ICUs), (Kwak et al., 2010). VAP is the most common nosocomial infection in general ICUs, and represents 31% of all ICU-acquired infections (Rello et al., 2002). It is also a leading cause of morbidity with rates of associated mortality ranging from 20% to 70% (Bouza et al., 2006).

Ventilator-associated pneumonia, the second most common healthcare-associated infection in pediatric intensive care units, accounts for 20% of nosocomial infections (Elward, 2003). Defined as pneumonia developing later than 48h after intubation and initiation of mechanical ventilation (MV), VAP is associated with morbidity and mortality (Langley and Bradley, 2005). Significant morbidity is reported between 3.7 and 10.0 additional ventilation days in neonates and children, resulting in prolonged admission and hospital costs (Richaradson et al., 2010).

An established relationship exists between VAP and aspiration of colonized oropharyngeal secretion, due to inadequate glottic closure around ETTs, especially in those nursed supine. Suctioning has also been implicated in VAP through direct contamination due to inadequate hand washing (Berdal et al., 2007). This work aimed to study characteristics and possible risk factors for the development of VAP, in critically ill neonates.

2. Patients and Methods:

The present study was carried at the NICU, during years 2010 to 2011, on 57 neonates who received MV, for more than 48h, because of different illnesses, Table 1.

Inclusion criteria:

A new radiographic infiltrate (> 24 h) or progressive infiltrates, 48h after initiation of ventilation till 48 h after extubation, with worsening of gas exchange, in the form of frequent desturations, increased oxygen requirements, or increased ventilator demands and at least three of the following criteria:

1. Temperature instability of unknown etiology.
2. Increased respiratory secretions, or increased suctioning requirements.
3. Apnea, tachycardia, nasal flaring, with retraction of chest wall, wheezes or rales.
4. Bradycardia (<100 beats/ min) or tachycardia (> 170 beats/min).

The diagnosis of VAP was established, using the CPIS. A CPIS of more than six was associated with a high likelihood of pneumonia (Fartouidi et al., 2003).

Methods:

All neonates were subjected to the following:

1. Case history and clinical examination, including;
   a) Vital signs and assessment of the gestational age, using modified Ballard scoring system. (Ballard et al., 1991)
   b) Clinical evidence of sepsis and preumonia, assessed with a sepsis score which included the following symptoms and signs; lethargy, diarrhea, vomiting, fever, jaundice, pyoderma, hypothermia, cyanosis, abdominal distention, seizures, conjunctivitis, significant apnea, tachypnea, and poor capillary refill. If the infant had 3 or more of the above signs and symptoms, septicemia was suggested (Tollner, 1982).
   c) Determination of postnatal age at which VAP developed.
2. Laboratory evidences of sepsis on study entry:
   a) Complete blood count (CBC) by counter apparatus.
   b) Quantitative serum C-reactive protein (CRP) by turbidimetry (Sanata, 2001).
   c) Blood culture on sulphonated broth media (Vandepitte, 1991).
3. Arterial blood gases (ABGs) and chest radiographs, done daily (or more frequently if indicated).
4. Non-bronchoscopic broncheo-alveolar lavage (NB-BAL) sampling (Aly et al., 2008):

Neonates diagnosed as having VAP were subjected to NB-BAL procedure, for bacteriological confirmation of the clinical diagnosis. Contraindications to the procedure included; high oxygenation requirement (FiO2 > 0.85), penumothorax, bradycardia, hypotension, and/or platelet count of < 30.000/mm^3.

A complete clinical examination and a chest radiograph were performed one hour after completion of sampling. Additional sedation was required if the baby was fighting the ventilator and FIO2 was increased just before the procedure (pre-oxygenation). The baby was positioned supine with the head turned 90° to the left to ensure that the suction catheter is advanced down the trachea and enters the right main bronchus. The obtained fluid was then collected in the sterile mucous trap and sent to the microbiology laboratory, for:

a) Macroscopic examination: The appearance of the speciemen was descriped regarding volume, color, consistency and aspect.
b) Microscopic examination: The number of white cells was estimated, using Gram stain.
c) Qualitative cultures of BAL.

Statistical analysis:

Data were entered, checked and analyzed using Epi-info (2000). Data were expressed as mean ± standard deviation (X ±SD), in quantitative variables, number and percentage for qualitative variables. Values of P< 0.05 were considered statistically significant (Dean et al., 2000).

3. Results:

As shown in table (1), indications for MV, in all neonates included RDS (40%), congenital pneumonia (30%), MAS (17.5%) and HIE (12.3%), with nonsignificant differences between VAP group and non-VAP group, (p=0.83).

Table (2) presents the demographic characteristics of both study groups. The mean gestational age and body weight were significantly lower among neonates with VAP than that in neonates with non-VAP (p =0.04 & 0.01, respectively) with nonsignificant difference regarding sex (p=0.75). The mean duration in NICU and on MV were significantly higher among VAP group than that among non-VAP group of neonates (p=0.03 & 0.001, respectively). Meanwhile, the use of invasive maneuvers (chest tubes/UVC) was significantly noted among the neonates with VAP (p= 0.001).

As shown in table (3), hypothermia, mucopurulent ETT secretions, radiological findings with progressive infiltrates were significantly observed in neonates with VAP than that in non – VAP neonates (p=0.04, 0.001 and 0.001, respectively). The use medications (inotrops and corticosteroids) was significantly noted among neonates with VAP than that among non-VAP

neonates (p=0.02 & 0.03, respectively), with nonsignificant differences, regarding the use of surfactant and antacids (p> 0.05).

Table (4) shows that there were significant differences between VAP and non-VAP groups regarding the mean serum CRP, serum albumin levels and positive blood cultures (p= 0.03, 0.02 & 0.018, respectively), with nonsignificant differences of other laboratory findings (p> 0.05). Positive blood cultures were detected in 49% (16/33) of neonates with VAP versus 29% (7/24) in neonates without VAP.

As shown in table (5), cultures of BAL obtained from 33 neonates with VAP revealed Gram negative organisms (*klebsiella pneumoniae*, *pseudomonas aeruginosa*, and *E.coli* in 23 (69.7%) neonates, Gram positive organisms (*staphylococcus aureus* and *pneumococci*) in 7 (21.2%) neonates, and *canndida albicans* in 3 (9.1%) neonates. Cross tabulation and correlation between blood cultures and BAL cultures, among VAP neonates shows nonsignificant similarity in the type of organisms cultivated from either blood or BAL (P = 0.49).

Table (1) Indications of mechanical ventilation in 57 neonates admitted to NICU, presented as number (n) and percent (%)

	Total n = 57	Patients (VAP) n = 33	Control(non-VAP) n = 24	χ^2	P value
RDS	23 (40.4%)	13 (39.4%)	10 (41.7%)	0.86	0.83 (NS)
Congenital pneumonia	17 (29.8%)	9 (27.3%)	8 (33.3%)		
MAS	10 (17.5%)	7 (21.2%)	3 (12.5%)		
HIE	7 (12.3%)	4 (12.1%)	3 (12.5%)		

NICU: neonatal intensive care unit χ^2 : Chi^2
RDS: respiratory distress syndrome NS: nonsignificant
MAS: mechonium aspiration syndrome. HIE: hypoxic ischemic encephalopathy.

Table (2) Demographic characteristics of 33 neonates with VAP versus 24 neonates without VAP.

Characteristic (s)	VAP n =33	Non-VAP n = 24	Test of significance	P- value
Gestational age (wks), X ±SD	33.6±3.2	35.7±1.6	"t" = 2.1	0.04 (S)
Body weight (g)	1500 ±870	2650±380	"t" = 24	0.01 (S)
Gender,n (%)				
Males	18 (54.5%)	11 (45.8%)	χ^2 = 0.1	0.75 (NS)
Females	15 (45.5%)	13 (54.2%)		
Mode of delivery, n (%)				
NVD	19 (57.6%)	13 (54.1%)	χ^2= 0.49	0.48 (NS)
C/S	14 (42.4%)	11 (45.8%)		
Duration in NICU (days), X ±SD	10.9 ±5.2	8.4±2.0	"t" = 2.19	0.03 (S)
Duration on MV (days), X ±SD	6.3 ± 1.67	4.7 ± 1.1	"t" = 4.1	0.001(S)
Invasive maneuvers, n (%)				
Chest tubes	9 (27.3%)	2 (8.3%)	χ^2 =14.56	0.001 (S)
UVC	25 (75.8%)	6 (25%)	χ^2= 13.87	0.001 (S)

VAP: ventilator associated pneumonia n: number %: percentage.
wks: weeks X ±SD: mean ±standard deviation χ^2: Chi2 g: gram
S: significant NS: nonsignificant
C/S: cesarean section NVD: normal vaginal delivery UVC: umbilical vein catheter

Table (3) Clinical characteristics and medications of 33 neonates with VAP versus 24 neonates without VAP, presented as number (n) and percent (%)

Characteristic (s)	VAP n =33	Non-VAP n = 24	χ^2	P- value
Hypothermia (temperature < 36.5°C)	19 (57.6%)	7 (29.1%)	1.26	0.04 (S)
Mucopurulent ETT secretions	24 (72.7%)	3 (12.5%)	21.4	0.001 (S)
Radiological findings	33 (100%)	- (-)	56.0	0.001 (S)
Medications:				
Inotrops (vasopressors)	29 (87.9%)	12 (50%)	6.32	0.02 (S)
Corticosteroids	13 (39.4%)	3 (12.5%)	4.37	0.03 (S)
Surfactant	6 (18.2%)	4 (16.6%)	0.02	0.88 (NS)
Antacids (H2 blocker)	27 (81.8%)	16 (66.7%)	3.5	0.06 (NS)

VAP: ventilator associated pneumonia ETT: endotracheal tube. χ^2: Chi^2

Table (4) Laboratory data of 33 neonates with VAP versus 24 neonates without VAP.

	VAP n = 33	Non- VAP n = 24	Test of significance	P- value
TLC (x10^3/mm^3), X±SD	19.1±7.8	16.55±3.4	"t" = 1.66	0.06 (NS)
Hb (g/dl), X ±SD	9.73±2.96	8.66±2.13	"t'= 1.57	0.11 (NS)
Platelet count (x10^3/mm^3), X±SD	148.7±61.2	185.7±89.4	"t"= 1.83	0.06 (NS)
C-reactive protein (mg/dl), X±SD	54.5±40.57	28.0±4.92	"t"= 1.18	0.03(S)
Serum albumin (g/dl), X±SD	2.6±0.53	3.06±0.49	"t" =2.92	0.02 (S)
Blood culture, n (%)				
Sterile	17 (51.5%)	17 (70.8%)	χ^2= 5.58	0.018(S)
Positive	16 (48.5%)*	7 (29.2%)**		

VAP: ventilator-associated pneumonia. n: number χ^2: Chi2 %: percent
X±SD: mean ± standard deviation mm^3: cubic millimeter mg: milligram g: gram
dl: deciliter TLC: total leucocytic count.
*: *klebsiella pneumoniae* 5 (15.2%), *staph aureus* 4(12.1%), *pseudomonas aeruginosa* 3 (9.1%), *E-coli* 3(9.1%) and *candida albicans* 1 (3%).
**: *klebsiella pneumoniae* 2(8.3%), *staph aureus* 2(8.3%), *pseudomonas aeruginosa, E-coli* and *Candida albicans*, each in 1 neonate (4.2%).

Table (5) Cross correlation between blood cultures and BAL cultures among 33 VAP patients.

		BAL culture						
	Organism	**Klebsiella pneumoniae**	**Candida albicans**	**Staph aureus**	**Pseudomonas aeruginosa**	**Pneumococci**	**E-coli**	**total**
Blood culture	No growth	7	2	3	4	0	1	17
	Klebsiella pneumoniae	0	1	1	1	0	2	5
	Candida albicans	1	0	0	0	0	0	1
	Staph aureus	1	0	0	1	2	0	4
	Pseudomonas aeruginosa	1	0	1	0	0	1	3
	E – coli	1	0	0	1	0	1	3
	Total	11	3	5	7	2	5	33

BAL: broncheo-alveolar lavage VAP: Ventilator-associated pneumonia
Pearson chi^2 = 4.39 P-value = 0.49 (nonsignificant)

4. Discussion:

Mechanical ventilation (MV) is an essential feature of modern NICU care. Unfortunately, MV is associated with a substantial risk of VAP (Aly et al., 2008), which represents the second most common nosocomial infection among patients in ICU and has the highest mortality rate (Shalini et al., 2009; Rebmann and Linda, 2010).

Two important processes are thought to be involved in the pathogenesis of VAP; bacterial colonization of the aero-digestive tract and the aspiration of contaminated secretions into the lower airway. The ETT is thought to play a prominent role in the development of these processes, not only by introducing oropharyngeal contents into the airway at the time of ETT placement in the airway, but also by serving as a "bridge" for bacteria to travel from the oropharynx to the lower airway. In addition, there is increasing evidence showing that the biofilm formed on the ETT surface may serve as a reservoir from which bacteria are continuously seeded into the lower respiratory tree (Pacheco-Flower et al., 2004).

Defining the infective organism causing VAP increases the accuracy of the clinical and radiological diagnosis. Hence, it helps modifying the initial antibiotics according to the culture and sensitivity tests and so preventing the emergence of resistant strains. Subsequently, the duration of ventilation, length of NICU stay and hospital expenses are markedly decreased. NB-BAL is used in neonates as it is a safe technique with few adverse effects (Koksal et al., 2006).

In the current study, CPIS was used for the diagnosis of VAP which is a diagnostic algorithm relying on easily available clinical, radiological and laboratory data in a weighted manner that makes it a reliable alternative for diagnosing VAP (Teixeria et al., 2007).

In this study, the demographic characteristics of neonates with and without VAP did not differ significantly as regard sex, diagnosis at admission and modes of delivery. Similar results were obtained by Duke (2005). On other hand, VAP rates were significantly increased with decreased body weight and decreased gestational age. Nearly similar results were reported by other studies (Petdachai, 2004; Chastre, 2005; Foglia et al., 2007). Furthermore, VAP was significantly associated with increased

duration of NICU admission, duration of MV and increased use of invasive maneuvers. Koksal et al (2006) stated that prolonged duration of MV generally increases the risk of infection due to exposure to other devices including nebulizers, humidifiers, and ventilator circuits. Meanwhile, the risk of VAP increases by 11% for every additional ventilator week (Apisarnthanarak, et al., 2003).

In this study, VAP was significantly associated with the presence of hypothermia, mucopurulent ETT secretions, radiological findings with progression of lung infiltrates, and use of inotrops and/or corticosteroids. Nearly similar results were obtained by Apisarnthanarak et al (2003), who reported that hypothermia and tachypnea are the most clinical symptoms associated with the development of VAP, and by Fischer et al (2000) who found that inotropic support is significantly more required in the VAP group. Furthermore, the use of corticosteroids is associated with the development of VAP (Foglia et al., 2007).

Out of the laboratory findings in our study neonates, increased mean serum CRP and hypoalbuminemia are significantly associated with the development of VAP. Failure of CRP levels to fall suggests infectious complication or ineffective or inappropriate treatment (Povoa et al., 2005). Alp et al (2004) stated that the inflammatory cascade leads to a common pathway, causing generalized increase in the vascular permeability (capillary leak syndrome), which leads to leakage of protein rich fluid into the interstitium. This appears to be the primary cause of hypoalbuminemia in sepsis.

In this study, microorganisms associated with blood stream infection in neonates with VAP, were *klebsiella pneumoniae* (15.2%), *staph aureus* (12.1%), *pseudomonas aeuginosa* (9.1%), *E-coli* (9.1%) and *candida albicans* in 3% of positive blood cultures. Meanwhile, blood culture was sterile in (51.5%) of neonates. NB-BAL cultures reported that gram negative bacteria were isolated from the majority of neonates with VAP (69.7%), with *klebsiella pneumoniae* predominating the positive cultures (33.3%). On the other hand, gram positive infection comprised (21.2%) of the total cultures, with *staph aureus* predominating the positive cultures, while *candida albicans* was positive in 9% of samples. Nearly similar results were reported by other studies (Koksal et al., 2006; Petdachai, 2004; Apisarnthanarak, et al., 2003). However, the reported species isolated differed from a study to another. This can be explained by the fact that the distribution of microorganisms differs from a NICU to another and also differs within same place from one period of time to another.

In this study, non of the studied neonates who developed VAP had the same organism that caused their blood stream infection. This is in agreement with other studies (Apisarnthanarak, et al., 2003; Yuan et al., 2007).

Infection preventionists play a key role in a hospital VAP prevention programme. Their role includes policy development, consultation on best practices, surveillance, risk assessment, education, communication, and facilitation of quality improvement projects to lower VAP rates in their facility (Rebmann & Linda, 2010).

Recommendations:

1) Strict training and supervision of infection control protocols, 2) suctioning guidelines should be strictly followed in the NICU, 3) the use of disposable ventilator circuits should be encouraged, and 4) unnecessary invasive procedures should be limited.

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