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Original article

Incidence, risk factors, clinico-microbiological profile, change in ventilator settings needed and outcome of 135 ventilator associated pneumonia cases in pediatric intensive care unit (PICU) of a tertiary care centre in Eastern India

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Abstract

Introduction: Ventilator associated pneumonia (VAP) is the second most common nosocomial infection diagnosed in mechanically ventilated patients with incidence of 20-36%, mainly caused by Gram-negative organisms in our country. Decrease in PaO_2/FIO_2 (arterial oxygen tension/fractional inspired oxygen) is an early marker of VAP. Impaired consciousness, re-intubation and continuous sedation are the most important risk factors of VAP. We aimed to study the incidence, risk factors, clinico-microbiological profile, change in ventilator settings needed and outcome of VAP in the pediatric intensive care unit (PICU) of a tertiary care centre in Eastern India.

Methods: This retrospective, observational study was conducted from January 2015 to June 2017, including 300 patients. We diagnosed VAP using Centre for Disease Control and Prevention (CDC) criteria and analysed the data using the Statistical Package for Social Sciences (SPSS®) version 20.0.

Results: Incidence of VAP was 45%, with higher incidence in infants with prolonged ventilation, use of continuous sedation and H2 blockers, re-intubation, presence of genetic syndromes and impaired consciousness. Gram-negative organisms (94%) (*P. aeruginosa* [45.93%], *K. pneumoniae* [25.18%], *E. coli* [14.81%], *Acinetobacter spp.* [8.14%]) outnumbered Gram-positive organisms (6%) (*S. aureus* [2.96%], *Enterococcus spp.* [2.22%] and *S. pneumoniae* [0.7%]). Resistance to common antibiotics was found in many cases. Multivariate analysis identified nasogastric tube

feeding (adjusted odds ratio [OR] = 1.88; 95% CI = 0.8-2.3), use of H2-blockers (adjusted OR = 2.04; 95% CI = 0.51-4.5), use of continuous sedation (adjusted OR = 2.779; 95% CI = 0.7-4.9), re-intubation (adjusted OR = 4.861; 95% CI = 1.6-17.8) and duration of ventilation > 1 week (adjusted OR = 5; 95% CI = 0.7-6.3) as the risk factors for VAP. Purulent tracheal secretions ($p < 0.0001$), positive tracheal aspirate culture ($p < 0.0001$) and a suggestive chest radiograph ($p < 0.0001$) were the strongest predictors of development of VAP. The PaO_2/FIO_2 ratio was lower in the VAP group in all the three points of comparison but was not significant. The tidal volumes, peak and mean pressures, positive end-expiratory pressures (PEEP) and FIO_2 were higher in VAP patients both on days 3 and 5 of ventilation as compared to non-VAP patients but the differences were not statistically significant. Duration of PICU stay (16.5 ± 10.1 days) and mortality (53.3%) was higher in VAP patients compared to non-VAP patients (11.5 ± 9.2 days and 40.6%).

Conclusion: Identifying and minimizing the risk factors and proper choice of antibiotics as per sensitivity would improve outcome. Characteristics and parameters of mechanical ventilation were not influenced by the development of VAP. The variables of ventilation would not be sensitive for diagnosing VAP and clinical, radiological and microbiological criteria remain the tools for diagnosing VAP.

Keywords

Nosocomial infection, mechanical ventilation, critical care.

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Introduction

Ventilator associated pneumonia (VAP) is the second most common nosocomial infection [1] diagnosed in mechanically ventilated patients with an incidence of 20-36% [2-4] in India. VAP is the nosocomial pneumonia in mechanically ventilated patients developing ≥ 48 hours after initiation of mechanical ventilation and was neither present nor incubating at the time of intubation [5]. VAP can be early onset (≤ 96 hours) or late onset (> 96 hours). Early onset VAP is commonly caused by community acquired pathogens such as *S. pneumoniae*, *C. pneumoniae* and *S. aureus*. Late onset VAP is caused by hospital acquired pathogens like *P. aeruginosa*, methicillin resistant *S. aureus*, *Acinetobacter spp.* and *Enterobacter spp.* Endotracheal intubation, the most important risk factor, increases the risk by 6-20 folds by acting as the primary route of bacterial entry [6] and hampering the natural defence like cough reflex. Infectious bacteria enter the lower respiratory tract via microaspiration, pooling and trickling of secretions around the cuff and development of biofilms on endotracheal tube within hours [7]. Prior antibiotic use, continuous enteral feeding, bronchoscopy [8], immunosuppressant drugs, neuromuscular blockade, re-intubation, gastric aspiration, mechanical ventilation for > 3 days, histamine type 2 (H2) receptor blockers [8], airway malformations, genetic syndromes and immunodeficiency are the other risk factors for VAP. New onset fever, change in consistency of tracheal secretions and decrease in PaO_2/FIO_2 ratio are the earliest markers of VAP [9]. VAP results in prolonged pediatric intensive care unit (PICU) stay and increased mortality and morbidity [10]. This first study from Eastern India on pediatric VAP primarily aimed to study the incidence, risk factors, clinico-microbiological profile and outcome and the secondary aim was to evaluate the change in ventilator settings required in VAP.

Materials and methods

We conducted this retrospective, observational study in the PICU of Dr. B.C. Roy Post Graduate Institute of Pediatric Sciences, Kolkata (West Bengal, India), from January 2015 to June 2017 and included 300 patients. We included patients aged 3 months-12 years, admitted in PICU and kept on mechanical ventilator for > 48 hours

in the study. Patients aged < 3 months, those having pneumonia at the time of PICU admission and those developing pneumonia in the first 48 hours of mechanical ventilation were excluded. Our study proforma included the patient particulars, the admitting disease, the indication of ventilation, the initial and subsequent changes in ventilator settings (positive end-expiratory pressure [PEEP], peak and mean pressures [P_{peak} and P_{mean}, respectively], tidal volumes [V_T], PaO_2/FIO_2 ratio), the treatment given (antimicrobials, neuromuscular and H2 blockers, sedatives and immunosuppressants), the clinical features (new onset fever, change in respiratory rate, chest retractions, change in character and consistency of tracheal secretions, adventitious sounds), the investigation reports (blood counts, cultures from blood and tracheal aspirates, chest radiograph and arterial blood gas [ABG]), progression and the outcome of the disease. All the patients had 45° head end elevation and chlorhexidine washes to maintain oral hygiene. The Centre for Disease Control and Prevention (CDC) criteria were used for diagnosing VAP.

Radiology signs

Two or more serial chest radiographs with at least one of the following:
- new or progressive and persistent infiltrates;
- consolidation;
- cavitation;
- pneumatoceles.

Clinical signs (vary with age)

In infants ≤ 1 year old

Worsening gas exchange, oxygen desaturations, increased requirement of supplemental oxygen or increased need for ventilation AND at least 3 of the following:
- fever (temperature > 38°C);
- leukopenia (< 4,000/mm^3) or leukocytosis (> 15,000/mm^3) and left shift (> 10% bands);
- new onset of purulent sputum, or change in character of sputum or increased secretions, or increased suctioning requirements;
- apnea, tachycardia, nasal flaring with retractions of chest wall or grunting;
- wheezing, crackles or rhonchi;
- bradycardia (< 100 beats/min) or tachycardia (> 170 beats/min).

For children > 1 year to ≤ 12 years

At least 3 of the following:
- fever (> 38°C or 100°F) or hypothermia (< 37°C or 97.7°F) with no other recognised cause;
- leukopenia (< 4,000/mm^3) or leucocytosis (> 15,000/mm^3);
- new onset or worsening cough, dyspnea, or tachypnea;
- crackles or bronchial breath sounds;
- worsening gas exchange, oxygen desaturations, and increased requirement of supplemental oxygen or increased need for ventilation.

Microbiological criteria

At least one of the following:
- positive growth in blood culture not related to another source of infection;
- positive growth in culture of pleural fluid;
- positive quantitative culture from minimally contaminated lower respiratory tract specimen: broncho-alveolar lavage (BAL) (> 10^4 colony forming units/ml) or protected specimen brushing (PSB) (> 10^3 colony forming units/ml);
- ≥ 5% BAL obtained cells with intracellular bacteria on direct microscopic examination after Gram-stain;
- histopathological evidence of pneumonia.

Endotracheal aspirates had been collected just following intubation and after 48 hours of ventilation, with aseptic measures using sterile DeLee mucous trap and the specimens were transported to the laboratory within one hour. In case of endotracheal aspirate culture, > 10^6 colony forming units/ml was considered significant for the diagnosis of VAP. The growth sensitivity was also done as per Clinical and Laboratory Standard Institute (CLSI) guidelines 2016.

Statistical methods

We divided all the children admitted during the study period into two groups – those with VAP and those without VAP. Their demographic, clinical, radiological and microbiological details were entered in Statistical Package for Social Sciences (SPSS®) version 20.0. We used descriptive statistics to calculate the frequencies of categorical data and to compute means and standard deviations (SD) of continuous variables. Chi-square test and Fisher exact tests were used for the analysis of categorical variables and student t-test to find the

difference between the means (SD) of continuous variables. P-value < 0.05 was considered statistically significant. Risk estimate was done by calculating the odds and risk ratios and their 95% confidence intervals (CI). We analyzed the probable risk factors for hospital-acquired pneumonia independently using the stepwise method in the multivariate logistic regression analysis. The following risk factors were analyzed: age ≤ 1 year, gender, genetic syndromes, re-intubation, nasogastric tube feeding, and the use of corticosteroids, neuromuscular agents, sedatives and H2-blockers.

Results

Results are presented in **Tables 1-8**.

Out of the 300 mechanically ventilated cases, 135 (45%) developed VAP. The mean age was 5.6 ± 4.2 years and 30% were infants. Male:female ratio was 1.3:1.

Bacterial growths were positive in 35 blood cultures and 151 tracheal aspirates. Among them, VAP was diagnosed in 15 and 113 cases respectively. Thus, growths from tracheal aspirates were more significantly associated with the development of VAP (p < 0.0001). Gram-negative organisms were predominant and *P. aeruginosa* was isolated in majority (45.93%) of the cases (**Tab. 2**).

All the organisms showed 100% sensitivity to colistin and imipenem except *Acinetobacter spp.* which showed resistance in 10% cases (**Tab. 3**).

All the organisms were sensitive to teicoplanin. *S. aureus* showed resistance to vancomycin and linezolid in 25% cases and to amoxycillin-clavulanate and cefuroxime in 50% cases. *Enterococcus spp.* was equally sensitive (67%) to linezolid, vancomycin, amoxycillin-clavulanate, cefuroxime and ciprofloxacin (**Tab. 4**).

Tab. 5 demonstrated that age ≤ 1 year (p = 0.0191), re-intubation (p < 0.0001), tube feeding (p = 0.0099), use of continuous sedation (p < 0.0001), H2 blocker prophylaxis (p = 0.0026,), genetic syndromes (p = 0.0125), and prolonged ventilation (p < 0.0001), were associated with increased risk of VAP. Gender, neuromuscular blockage and immunosuppressive therapy were not significantly associated with VAP. In the multivariate logistic regression model, the following variables were identified as independent risk factors for VAP: use of continuous sedation (adjusted odds ratio [OR] = 2.779; 95% CI = 0.7-4.9), re-intubation (adjusted OR = 4.861; 95% CI = 1.6-17.8) and duration of ventilation > 1 week (adjusted OR = 5; 95% CI = 0.7-6.3). All these factors had risk ratios > 1.

Purulent tracheal secretions (p < 0.0001), positive tracheal aspirate cultures (p < 0.0001) and a suggestive chest radiograph (p < 0.0001) were strong predictors of development of VAP. Fever (p = 0.2611), leucocytosis (p = 0.6185), leucopenia (p

Table 1. The indications of ventilation.

Causes	No. of patients	% of total
Neurological causes	180	60%
Encephalitis	90	30%
Meningitis	30	10%
Guillian-Barre syndrome	9	3%
ADEM	6	2%
Stroke	18	6%
Head trauma	9	3%
Status epilepticus	18	6%
Cardiac causes	48	16%
Congenital heart disease	30	10%
Myocarditis with congestive cardiac failure	18	6%
Gastrointestinal causes	30	10%
Acute pancreatitis	6	2%
Acute liver failure	3	1%
Post operative	21	7%
Infective diseases	30	10%
Complicated malaria	3	1%
Complicated dengue	9	3%
Severe sepsis	18	6%
Miscellaneous	12	4%
Snake bite	4	1.33%
Poisoning	5	1.67%
Complicated nephrotic syndrome	3	1%

ADEM: acute disseminated encephalo-myelitis; etiology of acute liver failure: Hepatitis A virus infection and Wilson's disease; post-operative cases: intestinal obstruction, enteric perforation, malrotation of gut, ruptured Meckel's diverticulum, ruptured appendix, and diaphragmatic hernia.

Table 2. The organisms and their frequency of occurrence.

Organism	Frequency (total = 135)	Percentage
P. aeruginosa	62	45.93%
K. pneumoniae	34	25.18%
E. coli	20	14.81%
Acinetobacter spp.	11	8.14%
S. aureus	4	2.96%
Enterococuccus spp.	3	2.22%
S. pneumoniae	1	0.7%

Table 3. The antibiograms of Gram-negative organisms (sensitivity).

Drugs	*P. aeruginosa*	*K. pneumoniae*	*E. coli*	*Acinetobacter spp.*
Colistin	62 (100%)	34 (100%)	20 (100%)	10 (90%)
Imipenem	62 (100%)	34 (100%)	20 (100%)	10 (90%)
Piperacillin-tazobactam	47 (75%)	17 (50%)	15 (75%)	5 (50%)
Cefotaxime	31 (50%)	17 (50%)	10 (50%)	5 (50%)
Cefepime	31 (50%)	27 (80%)	12 (60%)	8 (75%)
Cefoperazone-sulbactam	47 (75%)	26 (75%)	15 (75%)	8 (75%)
Ceftazidime	31 (50%)	17 (50%)	13 (65%)	5 (50%)
Amikacin	31 (50%)	20 (60%)	12 (60%)	5 (50%)
Ciprofloxacin	43 (70%)	26 (75%)	14 (70%)	8 (75%)

Table 4. The antibiograms of Gram-positive organisms (sensitivity).

Drugs	*S. aureus*	*Enterococcus spp.*
Linezolid	3 (75%)	2 (67%)
Vancomycin	3 (75%)	2 (67%)
Amoxycillin-clavulanate	2 (50%)	2 (67%)
Oxacillin	3 (75%)	1 (33%)
Cefuroxime	2 (50%)	2 (67%)
Ciprofloxacin	3 (75%)	2 (67%)
Teicoplanin	4 (100%)	3 (100%)
Tigecycline	4 (100%)	3 (100%)

= 1), and growths from blood cultures (p = 0.8576) were not significant predictors of VAP (**Tab. 6**).

In children with VAP, the mean duration of PICU stay was 16.5 ± 10.1 days compared to 11.5 ± 9.2 days in patients without VAP (p = 0.02). We found significant difference among VAP and non-VAP group with respect to stay ≤ 10 days versus > 10 days (p < 0.0001) and stay ≤ 20 days versus > 20 days (p = 0.003). Mortality was higher in VAP patients, but was not significant (p = 0.22).

The V_T, P_{peak}, P_{mean}, PEEP were higher in VAP patients both on days 3 and 5 as compared to non-VAP patients but the differences were not statistically significant. Interestingly, patients developing VAP had an overall decrease in PaO_2/FIO_2 ratio from day 0 to day 3 and from day 0 to day 5 whereas non-VAP patients had an overall increase in their ratios, but the magnitudes of the difference were not significant (**Tab. 8**).

Discussion

VAP is one of the most difficult challenges faced in modern PICUs with wide variation of incidence rates across the geographical regions due to differences in the diagnostic criteria used, variable sensitivity and specificity of the available diagnostic tests, lack of gold standard test for diagnosis of VAP, variability of hospital flora, PICU fumigation policy and maintenance of various equipment (warmers and ventilator machines), and differences in the age groups of study subjects (neonates, infants and children) in various studies. In our study, VAP had an incidence of 45%. Other pediatric studies reported incidence ranging from 30% to 46.4%. [1, 11, 12]. Gram-negative organisms (94%) were more often isolated than Gram-positive organisms (6%). *P. aeruginosa*, the most common causative agent, was found in 45.93% of cases followed by *K. pneumoniae* (25.18%), *E. coli* (14.81%) and *Acinetobacter spp.* (8.14%). *S. aureus*, *Enterococcus spp.* and *S. pneumoniae* had an incidence of 2.96%, 2.22% and 0.7%, respectively (**Tab. 2**). Bigham (Cincinnati Children's Hospital) [13], Gadani (Gujarat, India) [12], Dhadhke (Maharashtra, India) [11] and Elward (St Louis Children's Hospital) [14] found *Pseudomonas spp.* and Srinivasan (California) [15] and Foglia (Washington University School of Medicine, Missouri) [8] found *S. aureus* as the major organisms in their studies. A meta-analysis of pediatric VAP studies [16] found predominance of Gram-negative organisms in Asia and the most common pathogens were *Pseudomonas spp.*, *Acinetobacter spp.* and *Enterobacteriaceae spp.* Based on the sensitivity pattern of the isolates, we currently use imipenem and amikacin for Gram-negative organisms and vancomycin/linezolid for Gram-positive organisms as empirical therapy for VAP in our unit. Colistin, tigecycline and teicoplanin should be reserve drugs in non-responders (**Tab. 3** and **Tab. 4**). Delayed or inadequate treatment is associated with poorer outcomes, whereas polypharmacy can result in the emergence of new and more virulent strains [17].

Table 5. The risk factors for development of ventilator associated pneumonia (VAP).

Risk factors	Frequency of VAP	p-value (Chi-square test)	Odds ratio [a] (95% CI)	Risk ratio (95% CI)
Age ≤ 1 year	55/100	0.0191	1.725 (0.45-7.77)	1.1 (0.5-1.8)
Male gender	70/170	0.1304	0.7 (0.3-3.6)	0.82 (0.5-0.86)
Ventilation duration > 1 week	100/160	< 0.0001	5 (0.7-6.3)	2.5 (1.9-3.2)
H2 blocker prophylaxis	85/160	0.0026	2.04 (0.51-4.5)	1.5 (1.2-2.3)
Neuromuscular block	30/75	0.3495	0.761 (0.3-2.1)	0.85 (0.4-0.9)
Nasogastric tube feeding	70/130	0.0099	1.88 (0.8-2.3)	1.4 (0.9-2.3)
Re-intubation	80/118	< 0.0001	4.861 (1.6-17.8)	2.24 (1.97-3.66)
Genetic syndromes	18/26	0.0125	3.09 (0.7-5.9)	1.6 (0.9-1.9)
Immunosuppressive therapy	9/15	0.2900	1.892 (0.45-3.75)	1 (0.3-1.2)
Use of continuous sedation	76/128	< 0.0001	2.779 (0.7-4.9)	1.73 (1.4-2)

[a] Adjusted.
VAP: ventilator associated pneumonia.

Table 6. The clinical features and investigations.

Clinical features	Frequency of VAP	p-value	Odds ratio (95% CI)
Fever	120/235	0.2611	1.408 (0.9-4.5)
Leucocytosis	90/205	0.6185	0.8695 (0.3-3.7)
Leucopenia	40/89	1.0000	0.9967 (0.45-6.1)
Purulent tracheal secretions	127/182	< 0.0001	31.75 (15.2-46.4)
Opacities on chest radiograph	120/160	< 0.0001	25 (13.9-36.7)
Growth in tracheal secretions	113/151	< 0.0001	17.1662 (5.8-27.4)
Blood cultures	15/35	0.8576	0.906 (0.32-1.6)

VAP: ventilator associated pneumonia.

Table 7. The outcome of ventilator associated pneumonia (VAP).

		VAP patients	Non-VAP patients
PICU stay	**< 10 days**	35 (25%)	105 (75%)
	10-20 days	71 (61.2%)	45 (38.8%)
	> 20 days	29 (65.9%)	15 (34.9%)
Mortality		72/135 (53.3%)	67/165 (40.6%)

VAP: ventilator associated pneumonia; PICU: pediatric intensive care unit.

We found significantly higher incidence of VAP in infants with prolonged ventilation, use of continuous sedation, use of H2 blockers, tube feeding, re-intubation, presence of genetic syndromes and impaired consciousness (**Tab. 5**). Using multivariate analyses, several studies [10, 14, 15, 18-20] demonstrated that the risk for the development of VAP was 1.2-2 times higher for prolonged ventilation > 3 days, 3-13 times higher for tube feeding with large volume aspiration, 5-9.5 times higher for re-intubation, 2.5-77.5 times higher for the use of sedatives, 3.9 times higher for decreased level of consciousness and 2.4 times higher for genetic syndromes. Enteral nutrition is preferred over parenteral nutrition because of less risk for infectious complications related to the use of central venous catheters. However, use of gastric feeding tubes leads to an increased risk for gastro-esophageal reflux and aspiration, leading to the development of VAP. Continuous administration of feedings may cause lasting changes in gastric pH, predisposing the patient to the proliferation of bacteria (in particular, Gram-negative bacteria), whereas intermittent feeds can lead to gastric distension, reflux, and aspiration. No consensus exists among researchers on the most appropriate method to administer enteral feedings in patients at risk for VAP [21]. Apart from H2 blockers, other drugs, including antihypertensives, antihistamines, anticonvulsants, antineoplastics, sympathomimetics, and diuretics, can cause changes in salivary flow, the swallowing reflex, the ability to deliver self-care, systemic and local immune system functioning, and the physical and chemical properties of the microbial flora by modifying the microbial colonization of the oral cavity, thus predisposing patients to VAP [21]. Interestingly, Kusahara et al. [21] found significant association between the use of vasoactive drugs and the occurrence of VAP. Possibly, the use of inotropes reflects the unstable hemodynamic status that necessitates relatively long periods of mechanical ventilation and admission to the PICU, which themselves favors the development of VAP. Re-intubation is a significant risk factor for VAP, aspiration of gastrointestinal contents during this procedure being the most likely mechanism of infection. Additionally, the use of aseptic

Table 8. Ventilator settings of ventilator associated pneumonia (VAP) and non-VAP patients.

		Day 0 (D0)	Day 3 (D3)	Day 5 (D5)	Δ (D3-D0)	Δ (D5-D0)
V_T (ml/kg)	VAP	9.3 ± 3.2	9.5 ± 3.1	8.5 ± 3.5	0.2 ± 3.1	-0.8 ± 3.1
	Non-VAP	8.3 ± 3.1	8.2 ± 2.7	7.5 ± 3.0	-0.1 ± 3.0	-0.8 ± 2.9
p-value		0.8433	0.7818	0.8484	0.9509	1
t		0.2245	0.3162	0.2169	0.0695	0.000
95% CI of the difference		-18.170 to 20.170	-16.388 to 18.988	-18.834 to 20.834	-18.26 to 18.86	-18.26 to 18.26
Vt_E (ml/kg)	VAP	11.1 ± 2.7	10.4 ± 3.1	10.5 ± 2.2	-0.7 ± 2.6	-0.6 ± 2.5
	Non-VAP	11.0 ± 3.1	10.5 ± 3.2	10.2 ± 2.3	-0.8 ± 3.1	-0.8 ± 3.1
p-value		0.8875	0.9841	0.9335	0.982	0.9645
t		0.1601	0.0224	0.0943	0.0247	0.0502
95% CI of the difference		-15.528 to 16.728	-19.270 to 19.070	-13.394 to 13.994	-17.30 to 17.50	-16.93 to 17.33
P_{mean} (cm of H_2O)	VAP	11.9 ± 3.8	12.5 ± 3.9	12.9 ± 4.0	0.6 ± 3.8	1 ± 3.9
	Non-VAP	9.5 ± 3.7	10.1 ± 3.1	11 ± 4.1	0.6 ± 3.6	1.5 ± 3.7
p-value		0.6952	0.6776	0.7716	1	0.9344
t		0.4525	0.4817	0.3317	0.000	0.0930
95% CI of the difference		-20.420 to 25.220	-19.036 to 23.836	-22.746 to 26.546	-22.52 to 22.52	-23.63 to 22.63
P_{peak} (cm of H_2O)	VAP	27.5 ± 8.2	29.3 ± 8.5	30.3 ± 6.2	1.8 ± 8.1	2.8 ± 8.1
	Non-VAP	25.2 ± 10.1	27.1 ± 8.2	28.9 ± 9.1	1.9 ± 9.7	3.7 ± 9.9
p-value		0.8760	0.8694	0.9444	0.9944	0.9503
t		0.1768	0.1863	0.0788	0.0079	0.0704
95% CI of the difference		-53.676 to 58.276	-48.617 to 53.017	-48.271 to 50.071	-54.47 to 54.27	-55.93 to 54.137
PEEP (cm of H_2O)	VAP	5.6 ± 1.4	6.2 ± 1.4	6.6 ± 2.4	0.6 ± 1.4	1 ± 1.3
	Non-VAP	5.5 ± 1.5	5.7 ± 1.6	5.5 ± 1.4	0.2 ± 1.5	0.0 ± 1.5
p-value		0.9656	0.8360	0.7304	0.8634	0.6644
t		0.0487	0.2352	0.3959	0.1949	0.5038
95% CI of the difference		-8.728 to 8.928	-8.648 to 9.648	-10.855 to 13.055	-8.42 to 9.22	-7.54 to 9.54
PaO_2/FIO_2 (mm of Hg)	VAP	250 ± 67	248 ± 71	240 ± 83	-2 ± 67	-10 ± 67
	Non-VAP	272 ± 70	280 ± 83	282 ± 98	8 ± 70	10 ± 70
p-value		0.8415	0.7971	0.986	0.9862	0.8556
t		0.2270	0.2930	0.0198	0.0195	0.2064
95% CI of the difference		-438.91 to 394.91	-501.96 to 437.96	-437.67 to 433.67	-444.42 to 440.42	-436.91 to 396.91

VAP: ventilator associated pneumonia; V_T: tidal volume; Vt_E: expiratory minute ventilation; P_{peak}: peak inspiratory pressure; P_{mean}: mean airway pressure; PEEP: positive end-expiratory pressure; PaO_2/FIO_2 ratio: arterial oxygen tension/fractional inspired oxygen; D0, D3 and D5: day 0, day 3 and day 5 of ventilation respectively; Δ: difference.

technique may not be possible during emergency invasive procedures because of the critical nature of the situation [4, 14]. Various procedures like tracheostomy, central venous catheterization, bronchoscopy, thoracocentesis and transfusions have also been associated with increased risk of VAP [9]. Like Bigham et al. [13], we did not find increased risk of VAP in immunocompromised patients, although, Fayon et al. [22] found that immunodeficiency and immunosuppression were independent risk factors for pediatric VAP.

Purulent tracheal secretions, new opacities on chest radiograph and positive growth from tracheal aspirate were strong predictors of VAP (**Tab. 6**). However, fever, leukocytosis and leucopenia were not significant predictors of VAP. Hamid et al. [9] also found purulent tracheal secretions, tracheal aspirate cultures and suggestive chest radiograph as strong predictors of VAP.

PICU stay in VAP patients was significantly longer (16.5 ± 10.1 days compared to 11.5 ± 9.2 days in non-VAP patients) (**Tab. 7**). Mortality was higher in VAP patients (53.3%) as compared to non-VAP (40.6%) patients, but the difference was not significant. Hamid [9] too found that children with VAP had a significantly longer duration of ventilation and PICU stay, 13.5 ± 10.1 days in VAP compared to 7.7 ± 5.5 days in non-VAP patients. Multiple

studies have linked VAP to an increased duration of ventilation by 5-11 days and longer PICU stay by 20-34 days [22]. Almuneef et al. [23] also demonstrated longer PICU stay, but without statistically significant differences in mortality rates.

Our study is the first pediatric study investigating the changes in the mechanical ventilation settings with the development of VAP. The differences for each variable on days 0, 3 and 5 were calculated (**Tab. 8**), and we failed to prove any significant differences in their changes. Patients with VAP had been ventilated with higher tidal volumes as compared to non-VAP patients on days 3 and 5, but the differences were not significant. We interestingly found a decline in PaO_2/FIO_2 ratio progressively from 250 ± 67 mm of Hg on day 0 to 240 ± 83 mm of Hg on day 5 in VAP patients but the magnitude of the decline was not statistically significant when compared to non-VAP patients. P_{peak} and P_{mean}, FIO_2 and PEEP were also higher in the VAP group, the differences being insignificant. Similar results were found by Dennesen et al. in adults [24] and more pediatric studies are needed to authenticate the results. Our study suggests that variables of ventilation would not be sensitive for diagnosing VAP and clinical, radiological and microbiological criteria remain the tools for diagnosing VAP.

Our study had some limitations. Being retrospective, the data collection was restricted to information previously recorded. BAL and PSB could not be taken and we had to rely on tracheal aspirate for analysis. Moreover, this was a single centre study and since the diagnostic criteria vary from centre to centre the results of our study may not be generalized to others.

The most important aspect of nosocomial infections is prevention. Identification of the risk factors and predictors is imperative for the appropriate steps in this direction. A bundle approach [25] for preventing VAP includes the following strategies: hand hygiene, oropharyngeal decontamination with chlorhexidine, glove and gown use for endotracheal intubation, elevation of head end especially while tube feeding, avoidance of gastric over-distension, use of cuffed tube, daily assessment of readiness to be weaned from mechanical ventilation and use of weaning protocols, use of noninvasive ventilatory support whenever possible, minimizing the duration of mechanical ventilation, preference for orotracheal intubation over nasotracheal intubation, removing condensate from ventilator circuits, keeping the ventilator circuit closed during removal of condensate, changing the ventilator circuit only when the circuit was visibly soiled or malfunctioning and avoiding unnecessary tracheal suction.

Conclusions

What is already known?

In Asian PICUs, majority of VAP cases are caused by multi-drug resistant Gram-negative organisms, mainly affecting patients undergoing repeated intubations, prolonged ventilation, continuous sedation, H2 blocker prophylaxis, tube feeding, genetic syndromes, and lower age. VAP prolongs hospital stay and mortality and is not well predicted by fever or leucocyte counts.

What this study adds?

Purulent tracheal aspirate is the strongest predictor of VAP development. VAP patients require higher V_T and P_{peak} compared to non-VAP patients. PaO_2/FIO_2 ratios progressively decline in VAP patients and increase in non-VAP patients. However, the differences being statistically insignificant, the variables of ventilation would not be sensitive parameters for diagnosing VAP.

Declaration of interest

The Authors declare that there is no conflict of interest. Funding: nil.

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