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Incidence of ventilator-associated pneumonia, microbiology profile, and patient outcomes in a pediatric intensive care unit

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Abstract

Background: Ventilator-associated pneumonia (VAP) is defined as nosocomial pneumonia that develops in patients who have been on mechanical ventilation for more than 48 hours. This study aimed to determine the bacteriological profile of VAP in the pediatric intensive care unit (PICU) as well as patient outcomes in a hospital in India.
Methods: The study included 190 children (99 males and 91 females) aged 1 month to 12 years who were either manually or mechanically ventilated in a PICU. Clinical characteristics, microbiological profile, intubation details, complications, and outcomes were recorded. Blood and endotracheal aspirate were collected from VAP suspects and semi-quantitatively processed using standard microbiological techniques.
Results: Septic shock, bronchopneumonia, acute encephalopathy, acute central nervous system infection, congenital heart disease, and snake envenomation poisoning were diagnosed in 57, 41, 23, 15, 11, and 7 cases, respectively. The most common neurological causes were status epilepticus, neuromuscular diseases, and raised intracranial pressure. Nosocomial pneumonia (16%) and air leak (8.9%) were the most common complications in ventilated children. There was a 10% mortality rate among children in PICU. There were 100 VAP suspects, with 33 developing VAP. There were 11 children with early-onset VAP (<4 days) and 22 children with late-onset VAP (>4 days). Pathogenic microorganisms were isolated from 31 intubated children who were suspected of having VAP. Klebsiella pneumoniae was the predominant isolate from both early-onset and late-onset VAP cases. The majority of deaths were related to infection with Acinetobacter baumannii. Gram-negative isolates from early-onset VAP showed sensitivity to meropenem (87.5%), piperacillin-tazobactam (75%), and ciprofloxacin (62.5%). Enterobacteriaceae isolates from late-onset VAP showed susceptibility to meropenem (82%) and piperacillin-tazobactam (27%).
Conclusion: Infection with A. baumannii may be a risk factor for death in children with VAP. The most common pathogens isolated from children with VAP are K. pneumoniae and A. baumannii.

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Highlights:

What is current knowledge?
Ventilator-associated pneumonia (VAP) is associated with pathogenic microorganisms in the pediatric intensive care unit.

What is new here?
The most common pathogens isolated from children with VAP are K. pneumoniae and A. baumannii, which may be a risk factor for death in children with VAP.

Introduction

Ventilator-associated pneumonia is defined as a new infiltrate chest X-ray combined with positive microbiology findings from the lower respiratory tract and/or two or more positive clinical signs of pneumonia including inflammation and gas exchange impairment (1,2). It is the second most common cause of nosocomial infection in children, after catheter-associated bloodstream infection, and accounts for 15- 20% of total hospital-acquired infections.

According to a study (2), 10% of patients on mechanical ventilation develop VAP, and 13% of those are fatal. The incidence of VAP among children in pediatric intensive care units (PICUs) is reported to be between 2 and 5% around the world (3-6). In a study in the USA, Srinivasan et al. reported a 32% incidence according to the diagnostic criteria by the Centers for Disease Control and Prevention (7). Children requiring ICU care are more vulnerable due to their frequent need for intubation and prolonged mechanical ventilation, besides their susceptibility to hospital-acquired infections. The risk of VAP increases by 3% per day for the first 5 days of ventilation, then by 2% per day for the next 6-10 days, and finally by 1% per day after 10 days (8). Generally, VAP has been classified into early-onset (occurs within 96 hours of mechanical ventilation) or late-onset (occurs after 96 hours of mechanical ventilation). Because late-onset VAP is mostly caused by multi-drug resistant pathogens, early-onset VAP has a better prognosis (9). Early-onset VAP pathogens include Enterobacteriaceae, Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, and Candida species, whereas late-onset VAP pathogens include non-fermenting Gram-negative microorganisms such as Pseudomonas species and Acinetobacter species. Acinetobacter species are becoming more common as causes of opportunistic nosocomial infections. It is linked to a 70% mortality rate in patients with ICU-acquired pneumonia. It is also associated with a 70% resistance rate to 3rd generation cephalosporins, quinolones, and aminoglycosides, as well as an 87% resistance rate to multiple drugs. The prevalence of multi-drug-resistant Acinetobacter species is on the rise (10,11). Hence, it is critical to conduct periodic reviews, understand the local microbial flora, and determine susceptibility patterns in order to provide more effective treatments. This study was undertaken to detect the bacterial agents causing VAP in PICUs, their antimicrobial susceptibility patterns, and patient outcomes.

Methods

- ***Study design and population***

A descriptive study was carried out at the PICU of Narayana Medical College, Nellore, A.P. India from February 2018 to February 2020. Children aged 1 month to 12 years who were either manually or mechanically ventilated in PICU were included in the study. Those who were ventilated for <12 hours and referred cases were excluded. All sick children were evaluated at the Pediatric Emergency Department and initial stabilization of the patient, including intubation if necessary, fluid resuscitation, and inotrope initiation, was performed as needed. If no ventilator was available, the children were manually ventilated by their caregivers for varying periods until a ventilator became available. The children were managed on mechanical ventilation once the ventilators were available. The children were clinically monitored, with periodic cardiopulmonary assessments, oxygen saturation, and arterial blood gases as needed.

- ***Sample collection***

Endotracheal aspirate (ETA) was collected from VAP suspects in a sterile screw-capped container using aseptic precautions. Suction catheter size 8F was used for a 3.5 mm endotracheal tube (ETT), while 6F was used for 3 mm or smaller ETTs. The suction catheter was then advanced into the ETT until 1

cm beyond the tip, and 0.5 ml of normal saline was instilled into the endotracheal tube, aspirated, and then sent to the laboratory within 1 hour of collection. Strict aseptic procedures were used to collect blood samples (12). Before collecting the sample, the skin around the venipuncture site was thoroughly cleaned with 70% ethyl alcohol and allowed to dry for at least a minute (omitted iodine step in children, lean 2 additional times with 70% ethanol). An amount of 0.5-1.5 ml blood was collected in Brain Heart Infusion broth (13).

A smear was prepared from the ETA for direct Gram staining and examined for the presence of squamous epithelial cells, polymorphonuclear cells, and microorganisms (14).

- ***Bacterial culture***

The samples were inoculated into blood agar and MacConkey agar plates and then incubated aerobically overnight at 37 °C. Samples cultured on chocolate agar were incubated overnight at 37 °C with 5% CO2. The preliminary identification of organisms was done by colony morphology, Gram staining, motility, catalase test, and oxidase test. Further identification of organism was performed by standard biochemical tests such as the indole test, triple sugar iron agar test, methyl red test, citrate utilization test, urease test, mannitol motility medium, oxidative–fermentative test, and coagulase test for Gram-positive organisms. Standard quality control was done using ATCC strains, and antimicrobial susceptibility testing was done according to the Clinical and Laboratory Standards Institute (CLSI) guidelines 2019 (15).

- ***Antimicrobial susceptibility testing***

Antimicrobial susceptibility testing was done by using a modified Kirby Bauer's disc diffusion method on Mueller Hinton agar based on the CLSI guidelines M100 (16,17). The antibiotics used based on the CLSI guidelines M100 were as follows: penicillin (10 units), erythromycin (15 µg), vancomycin, linezolid (30 µg), cotrimoxazole (1.25/23.75 µg), and ciprofloxacin (5 µg) for Staphylococcus aureus; ampicillin (10 µg), amoxicillin-clavulanic acid (20/10 µg), gentamicin (10 µg), cefazolin (30 µg), amikacin (30 µg), ceftriaxone (30 µg), ciprofloxacin (5 µg), cotrimoxazole (1.25/23.75 µg), piperacillin-tazobactam (100/10 µg), cefoperazone-sulbactam (75/30 µg), imipenem (10 µg), and meropenem (10 µg) for Enterobacteriaceae.

- ***Data collection and analysis***

Before intubation, heart rate, respiratory rate, blood pressure, and oxygen saturation were measured. Ventilation details such as invasive or non-invasive ventilation, manual/mechanical ventilation, duration of ventilation, the need for re-intubation and the reason, and weaning methods were recorded. The outcomes were determined in the form of discharge, death, and against medical advice.

Categorical data were expressed statistically as absolute counts and percentages. Mean and standard deviation were used to express continuous data. For categorical variables, the Chi-square test was used. The independent t-test was used to analyze continuous variables. All tests were carried out at a p-value of <0.05. All analyses were done in SPSS (Version 18.0).

Results

Forty percent of PICU admissions met the inclusion criteria. Overall, 99 male and 91 female children (male-to-female ratio of 1.09:1.0) were included in the study. The majority of children (46.3%) were aged 1 to 12 months, while others were aged 13 to 60 months (33.7%) and >60 months (20%).

Septic shock was diagnosed in 57 cases (30%), bronchopneumonia in 41 cases (21.58%), and acute encephalopathy in 23 cases (12.10%). Upon arrival, the majority of the children (76.6%) who were ventilated in the PICU required intubation (Table 1).

When an intensivist was available, 103 children (54.8%) underwent rapid sequence intubation. Other children were intubated using a sedative and/or analgesic combination. Circulatory dysfunction, which included septic shock, congenital heart disease with cardiogenic shock, etc., was the most common clinical indication for intubation (37.8%). The most common neurological causes were status epilepticus, neuromuscular diseases, and raised intracranial pressure (34.6%).

The average length of mechanical ventilation was 5.3 ± 5.5 days (range: 1-16 days) (Table 2). Among children who received both manual and mechanical ventilation, 61 (81.3%) were ventilated for ⩾48 hours. The average duration of manual ventilation before mechanical ventilation was 1.3±1.2 days, and the duration of mechanical ventilation ranged from 12 hours to 42 days, with a mean duration of 4.5±6 days. T-piece weaning was the most common method (57.3%), followed by synchronized intermittent mandatory ventilation (7.9%), and continuous positive airway pressure (4.5%). However, 27 children (30.3%) were spontaneously extubated. A total of 32 (17%) children required re-intubation for various reasons, with tube displacement being the most common, followed by extubation failure.

As shown in Figure 1, nosocomial pneumonia was the most common complication (16%) in ventilated children, followed by air leak (8.9%). Two (1.1%) children had tracheostomies, which were performed due to the need for prolonged ventilation. Inotropes were required by 173 children (91.1%). To stabilize the patients, inotropes such as dopamine, dobutamine, epinephrine, and norepinephrine were administered in the Pediatric Emergency Department or the PICU. A total of 33 children (17.4%) had raised intracranial pressure symptoms. In our study, 10% (n=19) of the patients expired. There was a significant increase in mortality in the manual ventilation group among the children who were ventilated for more than 48 hours (p=0.01). In addition, 15 children died as a result of an air leak (Table 2). The presence of an air leak was found to be significantly associated with mortality. In ventilated children, re-intubation was a major risk factor for nosocomial pneumonia.

Table 1. Basic characteristics of children in PICU

Variables	Number of cases	Percentage
Septic shock	57	**30%**
Bronchopneumonia	41	**21.5%**
Acute encephalopathy	23	**12.1%**
Congenital heart disease	11	**5.7%**
Snake envenomation and poisoning	7	**3.6%**
Miscellaneous	36	**18.9%**
Indications for intubation		
Circulatory (1)	71	**37.8%**
Respiratory (2)	38	**20.2%**
Neurological (3)	65	**34.6%**
Circulatory + respiratory	7	**03.6%**
Circulatory + neurological	5	**02.7%**
Respiratory + neurological	2	**01.1%**
Tube size used		
Appropriate	185	**98.4%**
Small	3	**1.6%**
Route used		
Orotracheal	184	**97.9%**
Nasotracheal	4	**2.1%**
Types of invasive ventilation		
Manual ventilation	106	**56.4%**
Mechanically ventilated	7	**3.7%**
Combination of manual + mechanical ventilation	75	**39.9%**
Duration of ventilation		
≤ 48 hours	71	**66.9%**
48 hrs to < 7 days	34	**32.2%**
≥7 days	**1**	**0.9%**

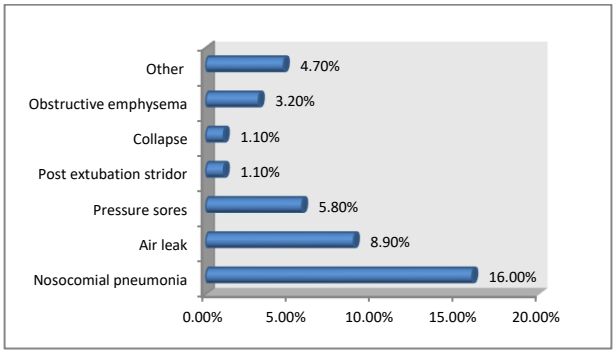

Figure 1. Complications developed in PICU

Table 2. Association of ventilation types with outcome, air leak and outcome, and intracranial pressure and outcome

Ventilation	Survived	Died	Total
Manual < 48 hours	62 (87.33%)	9 (12.67%)	**71**
Both < 48 hours	14 (92.86%)	1 (7.14%)	**14**
Mechanical < 48 hours	0 (0%)	1 (100%)	**1**
Manual 48 hours or more	30 (88.24%)	4 (11.76%)	**34**
Mechanical 48 hours or more	6 (100%)	0 (0%)	**6**
Both 48 hours or more	55 (93.23%)	4 (6.78%)	**59**
Non-invasive	2 (100%)	0 (0%)	**2**
Air leak and outcome			
Air leak n %	3 (16.67%)	15 (83.33%)	**18**
No air leak n %	165 (98.22%)	4 (1.785%)	**168**
Intracranial pressure and outcome			
Intracranial pressure	32 (80%)	8 (20%)	**40**
Without intracranial pressure	**139 (92.67%)**	**11 (7.33%)**	**150**

- ***Prevalence of VAP***

Of 190 children, there were 100 suspected VAP children, with 33 developing VA. Among the 33 children who developed VAP, 11 had early onset (within 4 days) and 22 had late onset (~ 4 days) VAP. A higher proportion of children developed late-onset VAP ($p<0.05$). Moreover, VAP developed in 20 of 56 intubated male children and 13 of 44 intubated female children. The most common reason for intubation was respiratory distress syndrome (24 cases) and sepsis (3 cases).

- ***Pathogens associated with VAP***

Among organisms isolated from ETA culture (n=100), pathogenic microorganisms (≥1 lakh colony-forming unit/ml) were isolated from 31 intubated children and colonizers from 21 suspected VAP children (colonizer <1 lakh colony-forming unit /ml). Thirty Gram-negative bacilli and one Gram-positive coccus were isolated from pathogens isolated from 31 laboratory-confirmed VAP cases. In addition, 3 children had septicemia caused by different organisms (Figure 2). The most commonly identified species were Klebsiella pneumoniae, followed by Acinetobacter baumannii, Candida species, and S. aureus (Table 3).

Table 3. Microorganisms isolated from blood culture of suspected VAP cases (n=40)

Microorganisms	Number of isolates
Klebsiella pneumoniae	16
Acinetobacter baumannii	8
Candida species	8
Staphylococcus aureus	8

Table 4. Microorganisms isolated from early-onset VAP cases (n=11)

Organisms	Number of isolates (n=11)	%
Klebsiella pneumoniae	7	**63.64**
Pseudomonas aeruginosa	1	**9.09**
Escherichia coli	1	**9.09**
Acinetobacter baumannii	1	**9.09**
Staphylococcus aureus	**1**	**9.09**

As shown in Table 4, K. pneumonia was the predominant isolated bacteria among both early-onset and late-onset VAP. Fatality rate was 63.6% among VAP cases and 29.86% among children without VAP.

A. baumannii was isolated using MacConkey agar culture (Figure 2).

Microorganisms isolated from blood culture (n=10) were K. pneumoniae (n=4), A. baumannii (n=2), and S. aureus (n=2).

As indicated in Table 5, Gram-negative bacilli isolated from blood culture were susceptible to meropenem (100%), piperacillin-tazobactam (50%), imipenem (83%), and cefoperazone-sulbactam (50%). Methicillin-resistant S. aureus (n=2) was sensitive to vancomycin and linezolid.

Table 5. Antimicrobial susceptibility pattern of microorganisms isolated from the blood culture of suspected VAP cases (n=10)

Microorganisms	Amp	G	Amc	AK	CTR	OF	CZ	COT	PIT	CFS	MRP
K. pneumoniae (n=4)	0	1	0	2	2	3	0	0	3	3	**4**
A. baumannii (n=2)	-	**0**	-	**0**	**0**	**1**	-	**0**	**0**	**0**	**2**

Piperacillin-Tazobactam (PIT); Imipenem (IPM); Meropenem (MRP); Ampicillin (Amp); Amoxicillin-Clavulanic acid (Amc), Gentamicin (G), Cefazolin (CZ), Amikacin (AK), Ceftriaxone (CTR), Cotrimoxazole (COT), Cefoperazone-sulbactam (CFS).

Table 6. Antimicrobial susceptibility pattern of microorganisms isolated from early-onset VAP

Microorganisms	Amp	AK	CTR	Amc	CIP	G	CZ	COT	PIT	CFS	MRP
***K. pneumoniae* (n=5)**	0	2	1	0	3	1	0	3	4	2	**4**
***P. aeruginosa* (n=1)**	-	0	0	-	0	0	-	-	0	0	**1**
***E. coli* (n=1)**	0	1	1	1	1	1	0	0	1	1	**1**
***A.baumannii* (n=1)**	-	1	0	-	1	1	-	0	1	2	**1**
Total (%)	**0**	**4 (50)**	**3 (37.5)**	**1 (12.5)**	**5 (62.5)**	**3 (37.5)**	**0**	**3 (37.5)**	**6 75**	**4 50**	**7 87.5**

Piperacillin-Tazobactam (PIT); Imipenem (IPM); Meropenem (MRP); Ampicillin (Amp); Amoxicillin-Clavulanic acid (Amc), Gentamicin (G), Cefazolin (CZ), Amikacin (AK), Ceftriaxone (CTR), Cotrimoxazole (COT), Cefoperazone-sulbactam (CFS).

Gram-negative isolates from early-onset VAP were sensitive to meropenem (87.5%), piperacillin-tazobactam (75%), and ciprofloxacin (62.5%) (Table 6). Moreover, K. pneumoniae isolates from late-onset VAP were susceptible to meropenem (82%) and piperacillin-tazobactam (27%) (Table 7).

Table 7. Antimicrobial susceptibility pattern of isolates from late-onset VAP

Microorganism	Amc	Amp	G	AK	CTR	CIP	CZ	COT	CFS	PIT	MRP
***K. pneumoniae* (n=11)**	**1**	**0**	**3**	**3**	**2**	**2**	**0**	**0**	**2**	**3**	**9**

Piperacillin-Tazobactam (PIT); Imipenem (IPM); Meropenem (MRP); Ampicillin (Amp); Amoxicillin-Clavulanic acid (Amc), Gentamicin (G), Cefazolin (CZ), Amikacin (AK), Ceftriaxone (CTR), Cotrimoxazole (COT), Cefoperazone-sulbactam (CFS).

Discussion

Ventilator-associated pneumonia is the second leading cause of hospital-acquired infections, with the highest mortality rate. Neurological indications predominated in a study by Kendirli et al (17), whereas respiratory causes were the most common reasons for mechanical ventilation in a study by Indrajit et al. This study also showed that the most common reason for intubation and mechanical ventilation was circulatory dysfunction, including shock (18). In the present study, intubation was performed orotracheally in 97.9% and nasotracheally in 2.1% of children. Inconsistent with our findings, no nasotracheal intubation was required in a study by Da Silva et al. (19). In our study, 13 out of 106 children who were manually ventilated died. The average duration of mechanical ventilation was 4.6±5.9 days. During the PICU stay, a total of 181 children (96.3%) were manually ventilated, and 75 of them were mechanically ventilated after varying durations of manual ventilation. In a study by Kendirli et al. (17), the average duration of ventilation was 18.8±14.1 days, and the median duration of ventilation in the Da Silva et al. (19) study was 6.5 days.

In our study, 16% of ventilated children developed nosocomial pneumonia, which is lower than the rate reported by Kendirli et al (17.5%). Torres et al. (20) investigated the role of re-intubation in nosocomial pneumonia. After controlling for age, gender, and prior bronchoscopy, they discovered that re-intubation was a significant risk factor for nosocomial pneumonia. Ibrahim et al. (21) and Kollef et al. (22) also found similar results. Air leaks were found in 8.9% of our cases. Previous studies reported the prevalence of air leaks as 13.1% (17) and 6.9% (23). In the present study, VAP was found in 33% of children. This finding is consistent with the results of previous studies (24-27).

The prevalence of late-onset VAP (66.7%) was higher than that of early-onset VAP (33.3%). This is in line with the findings of a study by Tripathi et al. (31). In a study by Lamichhane et al., early-onset VAP was detected in 8.42% of babies, while late-onset VAP was found in 15.79% of the cases (28).

Pathogenic microorganisms were isolated from 94% of children who developed VAP (ETA-culture positive), while only 2 were clinically defined as VAP (Figure 2).

Gram-negative bacilli isolated from blood culture were all susceptible to meropenem, while the rate of susceptibility to piperacillin-tazobactam, imipenem, and cefoperazone-sulbactam was 50%, 83%, and 50%, respectively. Methicillin-resistant S. aureus (n=2) was sensitive to vancomycin and linezolid.

In a review by Erfani et al. (29), the prevalence of Gram-negative bacteria ranged from 60 to 97% with Acinetobacter spp., Pseudomonas spp., and Klebsiella spp. predominating.

In this study, K. pneumoniae was the most common isolate from early-onset VAP cases. This finding is in line with the findings of Fallahi et al. (30), which showed that the most common isolates from early-onset VAP were K. pneumoniae (68.1%) and Acinetobacter spp. (13.6%). Similarly, Tripathi et al. (31) reported Klebsiella spp. (32.8%) as the most frequently isolated microorganism from early-onset VAP.

Gram-negative isolates from early-onset VAP showed that were sensitive to meropenem (87.5%), piperacillin-tazobactam (75%), and ciprofloxacin (62.5%).

In our study, K. pneumoniae was also the most commonly isolated microorganism from late-onset VAP. This finding is in line with the results of Tripathi et al. (31). However, another study reported P. aeruginosa (33.3%) and K. pneumoniae (20.8%) as the predominant causes of late-onset VAP (32).

Enterobacteriaceae isolates from late-onset VAP cases showed susceptibility to meropenem (82%) and piperacillin-tazobactam (27%).

There was a 10% mortality rate among ventilated children in PICU. Da Silva et al. (19) and Indrajit et al. (18) reported mortality rates of 19.8% and 24%, respectively. The improper use of ventilation with unregulated pressures results in acute lung injury.

Conclusion

Based on our results, circulatory failure is the predominant reason for intubation, and septic shock is the most common clinical diagnosis. Most

children in our study were manually ventilated, which was linked to an increased risk of death, particularly when lasting for 48 hours or more. It is essential to understand the local antibiotic policy in order to begin early empirical treatment. Because of the emergence of multi-drug resistant Acinetobacter species in VAP, it is important to identify the organisms early and initiate appropriate antibiotic therapy to reduce morbidity and mortality in mechanically ventilated children.

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Ethical statement

The study protocol was approved by the Ethics Committee of Narayana Medical College, India (approval code: NMC/IEC/Paed/2017).

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

PP and VK conceived and designed the experimental design, contributed to drafting and revising the article. VK and PP are involved in patient recruitment and follow-up. ML performed the microbial assays. All authors read and approved the final version of the manuscript.

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Figure 2. A. Direct Gram smear from ETA of children showing Gram-negative coccobacilli. B. MacConkey agar plate showing non–lactose fermenting colonies of A. baumannii. C. Culture smear of A. baumannii showing Gram-negative coccobacilli. D. Growth of A. baumannii on blood agar

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