

Outcome of Ventilator-Associated Pneumonia in Children Post Cardiac Surgery: A Prospective Observational Study

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Abstract

Background Ventilator-associated pneumonia (VAP) is a serious complication in post congenital cardiac repair in children leading to high morbidity and mortality. We conducted this study with an aim to determine incidence, risk factors, and mortality of VAP in pediatric cardiac surgical patients.

Methodology This prospective observational study included 371 children aged less than 12 years who underwent elective cardiac surgery for congenital heart disease from March 2020 to September 2021. Patients were categorized into two groups: those with VAP and without VAP.

Results Out of 371 patients, 67 patients (18%) developed VAP. The VAP incidence density was 36.3 episodes per 1,000 mechanical ventilation days. Age less than 1 year ($p < 0.001$), prolonged preoperative hospital stay (odds ratio: 2.25; 95% CI: 1.11–4.52; $p = 0.007$), and higher RACHS1 (risk adjustment in congenital heart surgery) category, prolonged invasive mechanical ventilation ($p < 0.001$), delayed sternal closure, tracheostomy, reintubation, use of uncuffed ET tube, and peritoneal dialysis were associated with higher incidence of VAP. Total 86 tracheal samples were taken. Most frequently isolated microorganisms were *Acinetobacter baumannii* (43%) and *Klebsiella pneumoniae* (23%). Antibiotic resistance was alarming as *Acinetobacter* and *Klebsiella* species were highly resistant to commonly used broad spectrum antibiotics like cephalosporins, aminoglycosides, and carbapenems.

Conclusion VAP incidence in our study was 18% and VAP incidence density was 36.3 per 1,000 mechanical ventilation days. Patients with VAP had higher mortality (32%) as compared with patients without VAP (12%).

Keywords

- ▶ antibiotic resistance
- ▶ pediatric cardiac surgery
- ▶ ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) refers to hospital-acquired infection (HAI) of lung parenchyma occurring 48 hours or more after initiation of mechanical ventilation (MV).¹ In the pediatric intensive care unit (ICU) VAP is the second most common HAI accounting for approximately 20% of all HAI.²⁻⁴ VAP is commonly caused by hospital acquired pathogens like *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, *E. coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA).⁵⁻⁸

Risk factors for VAP in children include prolonged MV, reintubation, aspiration, use of H₂ antagonist, blood stream infection, age younger than 12 months, congenital immunodeficiency, burns, airway malformations, and genetic syndromes.^{4,9-11} Cardiac surgeries especially with cardiopulmonary bypass (CPB) trigger inflammatory responses leading to impaired lung function, resulting in high risk for VAP.¹²

Information about VAP in children after congenital heart surgery is scarce and further studies are need of the hour. Children are highly vulnerable to VAP post-cardiac surgery and occurrence of multidrug resistance (MDR) pathogens is very frequent as reported by Tang et al.² We conducted this study with the objective to determine incidence, risk factors, and mortality due to VAP in post cardiac surgical children and to study the causative microorganisms and their antibiotic resistance profile.

Material and Methods

Study Design

This prospective observational study was conducted in cardiac surgical ICU of Department of Cardiothoracic and Vascular Surgery of a tertiary care teaching Institute in North India from March 2020 to September 2021

Patient Selection

All children aged less than 12 years who underwent elective congenital cardiac repair with or without CPB were enrolled in this study. Patients who died within 48 hours of surgery, those on MV, on antibiotics for documented infection during preoperative period, and who underwent emergency surgery were excluded from the study.

Study Plan

Approval was obtained from Institute ethics committee for this prospective study. Written and informed consent was taken from the parents/guardians of the participating children. We collected patient's demographic data (age, gender, height, weight), comprehensive diagnosis (type of congenital heart disease), and laboratory investigations: white blood cell count (WBC), neutrophils (%), absolute neutrophil count (ANC), platelets, serum urea and creatinine, C-reactive protein (CRP), chest X-ray (CXR) and duration of preoperative hospital stay. During the intraoperative period following variables were recorded: CPB time, aortic cross clamp (ACC) time, total duration of surgery and RACHS-1 category

for different surgeries. Following data were collected in the postoperative period-WBC count, ANC, platelets, serum urea and creatinine, CRP and culture from lower respiratory tract (LRT) specimen and serial chest X Rays. Lower respiratory tract samples were collected through endotracheal suction, mini-BAL or BAL and sent for microbial analysis. Various postoperative variables such as duration of MV and ICU stay, delayed sternal closure, re-exploration, tracheostomy, peritoneal dialysis, re-intubation, and use of uncuffed ET tube were also analyzed.

Antibiotic Prophylaxis

First line antibiotics in the form of third generation cephalosporin (cefotaxime) and aminoglycoside (amikacin) were given 1 hour before surgical incision. Escalation and de-escalation of antibiotic was done according to infection status, culture and sensitivity, clinical condition, and MV. These are done according to our ICU protocol on antibiotics for surgical patients.

Diagnostic Criteria for VAP

Diagnosis of VAP was done according to center for disease control and prevention (CDC) guidelines. We diagnosed our patients as VAP positive, only if pathogens were yielded from LRT specimens. The patients were divided into two groups: patients with VAP and those without VAP.

Statistical Analysis

Data was analyzed using SPSS package 28 (IBM, IL, Chicago, United States). Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were expressed as frequency and/or percentage. Student's *t*-test was implemented to compare data between two groups (VAP and non-VAP). Univariate analysis was used in assessing the risk associations of VAP. Multivariate analysis was applied to confirm risk factors of VAP. *p*-Value <0.05 was considered significant and <0.001 was highly significant for risk factor associations.

VAP incidence was calculated as follows: (number of cases with VAP/total number of patients who received MV) \times 100 = VAP rate per 100 patients.

VAP incidence density was calculated as follows: (number of cases with VAP/number of ventilator days) \times 1,000 = VAP rate per 1,000 ventilator days.

Results

Out of 1,953 patients admitted to the ICU, 371 patients fulfilled the inclusion criteria, while 1,582 patients were excluded as per the exclusion criteria as shown in the flow diagram (\rightarrow Fig. 1).

Preoperative and Intraoperative Variables

As delineated in \rightarrow Table 1, the median age of patients with VAP was 0.17 years (2 months) and without VAP was 0.75 years (9 months). Fifty-four (14.6%) patients who developed VAP were younger than 1 year ($p \leq 0.001$). Median body

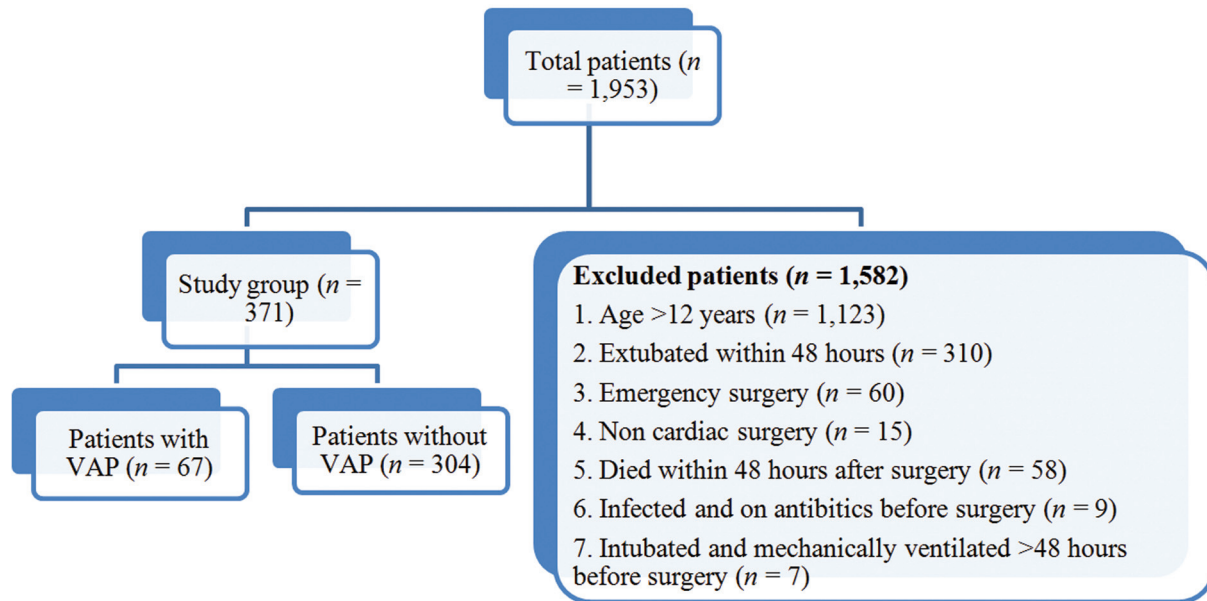


Fig. 1 Flow diagram showing study population and exclusion criteria.

weight of patients with VAP was 4.12 kg and patients without VAP was 7.20 kg. Fifty-eight (15.6%) male and nine (2.4%) female children developed VAP. Patients with longer duration of preoperative hospital stay had higher incidence of VAP (odds ratio [OR]: 2.25; 95% CI:1.11–4.52; $p = 0.007$). The mean CPB time in patients with VAP and without VAP was found to be 121.53 ± 57.71 and 99.19 ± 44.60 minutes, re-

spectively ($p = 0.0005$). The median duration of ACC time in patients with VAP was 75 minutes and without VAP was 67 minutes ($p = 0.0049$). The CPB time, ACC time, and total duration of surgery were found to be statistically significant and associated with higher risk of VAP. More number of patients from RACHS category 2 and 3 developed VAP in comparison to others (RACHS category 1, 4, and 5).

Table 1 Table showing demographic profile of study population, preoperative and intraoperative variables

Variables	Patients with VAP (n = 67) No. (%)	Patients without VAP (n = 304) No. (%)	p-Value
Age (years) ^a			<0.001
< 1 y	0.17 (0.01–10) 54 (14.6)	0.75 (0.01–12) 171 (45.7)	
1–6 y	12 (3.2)	101 (27.2)	
6–12 y	1 (0.27)	32 (8.6)	
Gender			0.053
Male	58 (15.6)	228 (61.5)	
Female	9 (2.4)	76 (20.5)	
Weight (kg) ^a	4.12 (2.45–29.5)	7.20 (2.50–36.7)	<0.001
Height (cm) ^b	62.32 ± 18.62	75.58 ± 26.34	0.0001
Preoperative hospital stay (days)	8 (0–41) ^a	4 (0–38) ^a	0.007
CPB time (min) ^b	121.53 ± 57.71	99.19 ± 44.60	0.0005
ACC time (min) ^a	75 (0–142)	67 (0–98)	0.0049
Total surgery duration (min) ^b	223.29 ± 33.14	173.41 ± 30.21	<0.001
RACHS-1 (mean ± SD)	2.86 ± 0.77	2.66 ± 0.80	0.003
Category 1	3 (0.8)	12 (3.2)	
Category 2	15 (4.0)	129 (34.7)	
Category 3	38 (10.2)	111 (29.9)	
Category 4	10 (2.7)	52 (14.0)	
Category 5	1 (0.3)	–	

^aMedian (min–max).

^bMean ± standard deviation.

Abbreviations: ACC, aortic cross clamp; CPB, cardiopulmonary bypass; RACHS-1, risk adjustment in congenital heart surgery.

Table 2 Table showing postoperative clinico-hematological, radiological, ventilatory parameters, and various risk factors associated with VAP

Variables	Patients with VAP (n = 67) No. (%)	Patients without VAP (n = 304) No. (%)	p-Value
Postoperative risk factors			
Mechanical ventilation (days) ^a	7 (2–27)	3 (2–29)	<0.001
Length of ICU stay (days) ^a	13 (4–55)	7 (4–37)	<0.001
Delayed sternal closure	15 (22.3)	24 (7.8)	0.001
Re-exploration	7 (10.4)	24 (7.8)	0.470
Tracheostomy	10 (14.9)	5 (1.6)	<0.001
Peritoneal dialysis	10 (14.9)	8 (2.6)	<0.001
Reintubation	13 (19.4)	12 (3.9)	<0.001
ET tube (uncuffed)	62 (92.5)	240 (6.7)	0.009
Clinical parameters			
Fever	39 (58.2)	37 (12.1)	<0.001
Increased respiratory secretion	40 (59.7)	33 (10.8)	<0.001
New onset crepitations	48 (71.6)	53 (17.4)	<0.001
Hematological parameters			
WBC count (10 ³ /μL) ^b	11.57 ± 5.19	8.45 ± 3.14	0.049
Neutrophils (%) ^b	64.61 ± 12.86	67.01 ± 14.20	0.203
ANC (10 ³ /μL) ^b	7.17 ± 2.82	7.36 ± 3.00	0.630
Platelet count (10 ³ /μL) ^a	3.38 (0.53–6.01)	2.47 (0.29–9.92)	0.563
Creactive protein (mg/L) ^a	10 (0.6–98)	9.96 (0.5–215)	0.710
Radiological findings			
Consolidation/infiltration/patch	44 (65.6)	30 (9.8)	<0.001
Ventilatory parameters			
Increased PIP	42 (62.6)	32 (10.5)	<0.001
Increased PEEP	5 (7.4)	11 (3.6)	0.181
Decreased PaO ₂ level	33 (49.2)	66 (21.7)	<0.001
Increased FiO ₂ requirement	51 (76.1)	51 (16.7)	0.535

Abbreviations: ANC, absolute neutrophil count; ET Tube, endotracheal tube; FiO₂: inspired fractional oxygen; PEEP, peak end expiratory pressure; PIP, peak inspiratory pressure; PaO₂, partial pressure of oxygen.

^aMedian (min–max).

^bMean ± standard deviation.

Postoperative Variables

As depicted in ►Table 2, prolonged MV, delayed sternal closure, tracheostomy, peritoneal dialysis and reintubation and use of uncuffed ET tube were found to be risk factors for VAP by multivariate analysis.

►Table 3 shows the results of logistic regression analysis adjusted for duration of preoperative hospital stay, CXR finding (consolidation/infiltration/patch), increased respiratory secretions, increased fractional inspired oxygen (FiO₂) requirement, blood stream, and urinary tract infections. The multivariate analysis found that OR for VAP was 2.25 (95% CI = 1.11–4.52) for preoperative hospital stay, 4.12 (95% CI = 1.79–9.49) for CXR finding (consolidation/patch/infiltration), 2.92 (95% CI = 1.31–6.49) for increased respiratory secretion, 4.46 (95% CI = 1.85–10.76) for increased FiO₂ requirement, 4.02 (95% CI = 1.57–

10.25) for blood stream infection, and 9.46 (95% CI = 1.86–48.13) for urinary tract infection.

Distribution of Pathogens

A total of 86 tracheal aspirate samples were taken from 67 patients and microbial analysis was done. The most frequently isolated microorganisms were *Acinetobacter baumannii* (43%) and *Klebsiella pneumoniae* (23%). Samples from all patients had growth of one or more microorganism. *Acinetobacter* and *Klebsiella* were 100% susceptible to colistin, but highly resistant to commonly used antibiotics such as amikacin, cefotaxime, ceftazidime, and meropenem. The resistance profile for *E. coli* was also alarming as they were highly resistant to cephalosporins and aminoglycosides but susceptible to colistin.

Table 3 Risk factors of VAP in children post cardiac surgery as found by multivariate logistic regression analysis

Variables	Odds ratio (95% Conf. interval)	Unadjusted odds ratio	p-Value
Prolonged preoperative hospital stay(days)	2.25 (1.11–4.52)	2.27	0.007
Consolidation/infiltration/patch (CXR)	4.12 (1.79–9.49)	17.47	0.001
Increased respiratory secretion	2.92 (1.31–6.49)	12.12	0.008
Increased FiO ₂ requirement (Hypoxia)	4.46 (1.85–10.76)	15.81	0.001
Blood stream infection	4.02 (1.57–10.25)	6.68	0.004
Urinary tract infection	9.46 (1.86–48.13)	3.80	0.007

Abbreviations: CXR, chest X-ray; FiO₂, fraction of inspired oxygen.

Outcome

Patients who developed VAP had longer duration of ICU stay and increased overall hospital stay. Mortality was high for the patients who developed VAP (32.8%) than those who did not develop VAP (12.8%). Multidrug resistant *Acinetobacter baumannii* was found to be the most common microorganism causing mortality among VAP patients ▶ **Table 5**.

Discussion

VAP has been a topic of profound interest in adults and pediatric population due to the high morbidity and mortality associated with it. But there is scanty literature in the prospective studies in particular pertaining to VAP in children undergoing congenital heart surgeries. Cardiac surgeries and CPB induce a cascade of changes that result in hemodynamic alteration, capillary leak syndrome due to cytokine surge and decreased pulmonary compliance and increased airway resistance. Consequently, the altered respiratory mechanics lead to prolonged invasive MV, tracheostomies, hemodynamic instability requiring longer duration and higher doses of inotropes and renal impairment, making these children highly vulnerable to VAP. In this study we focused exclusively on VAP in post cardiac surgical children in a high volume tertiary care teaching institute.

In this prospective observational study, the incidence of VAP was 18% and VAP incidence density was 36.3 per 1,000 MV days. This was higher in the study conducted by Tang et al where VAP incidence was 13% and VAP incidence density was 21.6 per 1,000 MV days.² But the authors Ghassan et al and Roeleveld et al reported the incidence of VAP in post cardiac surgical children as 7 and 8.8%, respectively which was much lower as compared with our study.^{13,14} The median age of patients with VAP was 0.17 years (2 months). 80.6% of the patients who developed VAP were children younger than 1 year. Pediatric population after cardiac surgery is at high risk of VAP due to younger age, malnutrition, and lower body weight. Use of invasive devices, invasive MV, invasive monitoring after cardiac surgery further increases the risk of VAP. CPB time, ACC time, and total duration of surgery were directly proportional to incidence of VAP as the extracorporeal circulation induces severe inflammatory changes in almost all organ systems causing

myocardial and pulmonary dysfunction. This was in concordance to that reported by Sahu et al.^{14,15} Tang et al have previously documented that complex CHD was associated with VAP after surgery.² In our study, RACHS-1 scoring was used to define complexity of surgical procedure. 10.2% of VAP patients belonged to RACHS 3 category ($p = 0.003$) in our study. Complex surgical procedures take longer time to recover in postoperative period, along with requirement of longer MV, invasive devices, high inotropic support, and multiple transfusions.

Prolonged MV ($p \leq 0.001$) was found to be an independent and modifiable risk factor for VAP in this study. Similar finding was reported in study by Tang et al (OR: 15.19; 95% CI: 2.15–107.2) and Awasthi et al (OR: 3.76; 95% CI: 1.41–10.02; $p = 0.008$).^{2,7}

Various risk factors of VAP (such as prolonged MV, delayed sternum closure, tracheostomy, reintubation, use of uncuffed endotracheal tube, peritoneal dialysis) have been identified as published in many studies.^{5,9,15} In our study we found that prolonged preoperative hospital stay, delayed sternum closure, tracheostomy, reintubation, use of uncuffed endotracheal tube and peritoneal dialysis were significantly associated with VAP in postoperative period.

Table 4 Different microorganisms isolated from lower respiratory tract secretions of patients with VAP—expressed in numbers and percentages

Microorganisms (n = 86)	No of isolates (%)
<i>Acinetobacter baumannii</i>	37 (43)
<i>Klebsiella pneumonia</i>	20 (23)
<i>Escherichia coli</i>	12 (14)
<i>Pseudomonas aeruginosa</i>	4 (5)
<i>Stenotrophomonas maltophilia</i>	3 (4)
<i>Burkholderia cepacia</i>	2 (2)
<i>Staphylococcus aureus</i>	2 (2)
<i>Serratia marcescens</i>	1 (1)
<i>Aspergillus</i>	4 (5)
<i>Cytomegalovirus</i>	1 (1)
Total	86

Table 5 Primary and secondary outcome in patients with VAP

Variables	Patients with VAP (n = 67) No. (%)	Patients without VAP (n = 304) No. (%)	p-Value
ICU stay (days)—secondary outcome	13 (4–55) ^a	7 (4–37) ^a	<0.001
Hospital stay (days)—secondary outcome	27 (4–134) ^a	18 (5–100) ^a	<0.001
Died	22 (32.8)	39 (12.8)	<0.001
Survived—(primary outcome)	45 (67.2)	265 (87.2)	

^aMedian (min–max).

Diagnosis of VAP was established according to CDC guidelines. However, microbiological confirmation from LRT secretions was a mandatory criteria in our study as infiltrates on CXR in cardiac patients can occur due to multiple other causes (infectious, fluid overload, atelectasis, and pleural effusion).

On the basis of LRT aspirate culture findings, we concluded that *Acinetobacter baumannii* (43%) and *Klebsiella pneumoniae* (23%) were the most frequently isolated pathogens causing VAP. The other organisms implicated in causing VAP were less frequent and are described in **Table 4**. In total, 5% of the children in our cohort had super-added fungal VAP caused by *Aspergillus* and some patients had polymicrobial infection too. However, in previous studies, most common etiological agents reported were *P. aeruginosa*, *S. aureus*, *H. influenzae*, and *M. catarrhalis*.¹⁶

Emergence of MDR to common broad-spectrum antibiotics like cephalosporins, aminoglycosides, and carbapenems was found to be major hurdle in pediatric post cardiac surgery patients. Similar findings were reported in studies by Sahu et al and Ensminger et al.^{15,16} VAP after cardiac surgery causes significant increase in MV duration, ICU stay, and hospital stay which add to the morbidity in the pediatric population and this study confirms these findings. Similar findings were reported in the studies by Tang et al, Ghassan et al, Roeleveld et al, and Sahu et al.^{2,13–15}

In this study we found that patients who developed VAP had a mortality of 32.8% and *Acinetobacter baumannii* was the most common pathogen causing death. High mortality of 38.4% was observed by Tang et al in his study.² Majority of patients who died were less than 1 year old. No neurological complication was noted after recovery from VAP. We thus emphasize that timely identification of risk factors, early diagnosis of VAP, appropriate treatment of VAP, and prevention of complications are needed to help these children convalescing better, earlier and reducing mortality rate.

The study had certain limitations. Though this study was conducted in a tertiary care high volume teaching institute, but because of the COVID pandemic we could not garner more number of patients as routine surgeries were interrupted often during the study period, and the total study population was less in number than expected and also because it was a single center study, thus the results cannot be generalized. None of our patients had corona virus infection pre or postoperatively.

Conclusion

VAP is the most common hospital acquired infection amongst pediatric cardiac surgical patients in our ICU with a mortality rate of 32.8%. The incidence of VAP in our study was 18% and VAP incidence density was 36.3 per 1,000 MV days which carried with it a high morbidity in terms of longer invasive ventilation, ICU, and hospital stay. Postoperatively high index of suspicion of clinical infection, combination of laboratory tests, radiological findings, and microbial cultures are helpful to diagnose and treat VAP-induced sepsis at an early stage. Implementation of VAP prevention bundle, strict implementation of infection control surveillance policies, and antimicrobial stewardship help in reducing the incidence of VAP and its high fatality.

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None.

Conflict of Interest
None declared.

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