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Original Article

Ventilator-associated pneumonia after pediatric cardiac surgery in southern Taiwan

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Background and purpose: To determine the frequency, risk factors, associated pathogens, and outcomes of ventilator-associated pneumonia (VAP) after pediatric cardiac surgery.

Methods: This was a retrospective review of the medical records of patients younger than 18 years with congenital heart disease (CHD) who underwent cardiac surgery from January 2005 to December 2007. Patients were categorized into 2 groups: with and without VAP.

Results: Of 100 patients, 13% acquired VAP. Most patients (85%) who developed VAP were infants younger than 1 year. Patients with complex CHD were more likely to develop VAP than patients with simple CHD ($\chi^2 = 7.69$; $p < 0.03$). Two independent and modifiable risk factors were identified: prolonged use of mechanical ventilation (adjusted odds ratio [AOR], 15.196; 95% confidence interval [CI], 2.158-107.2) and prolonged use of a central venous catheter (AOR, 7.342; 95% CI, 1.054-51.140). The cardiopulmonary bypass time and duration of chest tube drainage were not risk factors. The development of VAP increased pediatric intensive care unit duration of stay ($p < 0.006$), duration of hospital stay ($p < 0.001$), and mortality rate ($p < 0.001$). *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureu*s were the most common pathogens isolated from endotracheal aspirate.

Conclusions: VAP is common after congenital heart surgery. Physicians must pay special attention to infants with complex CHD because they are at high risk for the development of VAP after congenital heart surgery. Shortening the duration of mechanical ventilation and central venous catheter placement are critical factors for reducing the risk for VAP.

Key words: Intensive care units, pediatric; Pneumonia, ventilator associated; Thoracic surgery

Introduction

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in critically ill adult patients, and is the second most common after bloodstream infection for the pediatric population [1,2]. For patients requiring mechanical ventilation, the pneumonia rate is 6- to 20-fold higher than that for patients who do not require ventilator assistance [1,3]. Recent studies have reported that the frequency of VAP varies from 7% to 19% in adult patients and 9% to 21% in pediatric patients after cardiac surgery, and it is a leading cause of morbidity and mortality [4-7]. The pathogenesis of VAP is a result of the balance between host defenses and microbial propensity for colonization and invasion. A number of risk factors for the development of VAP after cardiac surgery in the adult population have been established and categorized as patient-related, infection control–related, or intervention-related [3]. Recently, the risk factors for children in intensive care units (ICUs) have also been reported, and include age younger than 12 months, congenital immunodeficiency, burns, transfusion, and genetic syndromes [2,6]. Information about VAP in

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children after congenital heart surgery is scarce and therefore additional study is needed.

Following heart surgery, children are at particularly high risk, and an increasing number of multidrug-resistant (MDR) pathogens in ICUs have also been reported [8]. These factors have recently alerted physicians to be more aware of VAP, as this infection increases the duration of pediatric ICU (PICU) and hospital stay, and has a direct impact on mortality and hospital costs [9].

This is the first report from Taiwan to describe children with congenital heart disease (CHD) after cardiac surgery. The study aimed to examine the incidence of VAP, the risk factors for VAP, outcomes associated with VAP, and the microbiological pathogens involved in the development of VAP. The study was conducted at Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, a 1390-bed tertiary teaching and referral hospital serving a population of approximately one-third (500,000) of the population of Kaohsiung, southern Taiwan.

Methods

Patients

All patients younger than 18 years with CHD who underwent cardiac surgery were included. Modified National Nosocomial Infection Surveillance System (NNISS) criteria [10,11] were used for the diagnosis of VAP. VAP was defined clinically as a new or persistent radiographic pulmonary infiltrate, consolidate, cavitation, or pneumatocele after 48 h of mechanical ventilation, associated with the development of 2 of the following conditions: fever (>38°C) without other recognized causes, leucopenia (white blood cells [WBC], <4000/μL) or leukocytosis (WBC, >12,000/μL), and new-onset purulent sputum with a positive Gram-stain finding. Patients who fit the modified NNISS criteria and the Clinical Pulmonary Infection Score were enrolled into the study [10].

Definitions

Early-onset VAP was defined as pneumonia occurring within the first 5 days of mechanical ventilation and late-onset VAP was defined as pneumonia occurring after ≥5 days of mechanical ventilation [10]. MDR *Pseudomonas aeruginosa* was defined as resistance to ceftazidime and at least 3 of the following antibiotics: piperacillin, cefoperazone, ceftazidime, imipenem, cefepime, cefpirome, ofloxacin, ciprofloxacin, minocycline, and aminoglycosides.

Design

Retrospective medical chart review was performed for all children younger than 18 years with CHD who underwent cardiac surgery from January 2005 to December 2007. Patients were separated into 2 groups of those with VAP and those without VAP. Both groups were compared and analyzed. Possible risk factors and outcomes associated with VAP were analyzed, including type of CHD, duration of preoperative days in the ICU, cardiopulmonary bypass time, duration of mechanical ventilation, days with central venous catheter placement, days with chest tube drainage, diaphragm paralysis, duration of postoperative stay in the ICU, duration of hospital stay, and mortality, as well as the characteristics of CHD and the microbial pathogens isolated from endotracheal aspirate. Antimicrobial prophylaxis for congenital heart surgery was cefazolin 25 mg/kg given intravenously 30 min prior to the first surgical incision, every 6 h during surgery, and postoperatively for 3 days. Gentamicin, at a dose of 3 mg/kg once per day, was also administered before and after the operation for 3 days.

Microbiological samples and Gram stain

Cultures from the respiratory tract were taken from all patients who were suspected of having VAP. A sterile technique was used to advance the catheter through the endotracheal tube and, once in position, suction was applied and the secretion obtained was collected directly into the trap and transported to the microbiological laboratory within 2 h. All microorganisms were identified by standard methods. Antimicrobial susceptibility was determined according to the recommendations of the Clinical and Laboratory Standards Institute [12].

Examination of Gram-stained smears obtained from the aspirate can also facilitate in the diagnosis. Routine Gram stain was performed in the PICU for all patients suspected of having VAP. Positive Gram-stain was defined as >25 WBC and <10 epithelium cells/100x field with phagocytosis on high-power field plus a high concentration of bacteria.

Statistical analysis

Descriptive data were summarized as mean ± standard deviation (SD) or standard error (SE), and percentages. When appropriate, 95% confidence intervals (CIs) were calculated. Chi-squared test was used to compare categorical variables and 2-tailed *p* values were reported. Continuous variables were compared

using *t* test, and the Mann-Whitney *U* test was used for non–normally distributed continuous variables. To determine the relationship between the development of VAP and the independent variables, including duration of cardiopulmonary bypass time, days of mechanical ventilator use, days of chest tube drainage, and days with central venous catheter placement, multiple logistic regression models were used to control for the effects of confounding variables. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS, Inc., Chicago, IL, USA); $p < 0.05$ was considered significant.

Results

111 consecutive patients with CHD who had undergone cardiac surgery during a 2-year period were evaluated. Eleven patients were excluded for the following reasons; 6 patients had patent ductus arteriosus (PDA) of prematurity and underwent bedside PDA ligation, 2 died during operation, 2 died in the ICU immediately after surgery, and 1 underwent pacemaker replacement. 100 patients were evaluated.

The mean age ± SD of the patients was 3.31 ± 5.4 years (range, 7 days to 18 years); 65 patients were younger than 1 year. There were 52 boys and 48 girls. The ratio for complex and simple CHD was 1.8:1. Table 1 shows the types of CHD.

Among the 9 patients who died, 8 (88%) had complex CHD and 7 (77%) were infants. The mean ± SD duration of cardiopulmonary bypass time was 92.3 ± 64.5 min. The mean ± SE duration of mechanical ventilator after cardiac surgery was 6.1 ± 14.0 days, with a mean ± SD duration of chest tube drainage of 5.6 ± 4.3 days and a mean ± SE duration of central venous catheter placement of 6.9 ± 7.2 days. The mean ± SE duration of stay in the ICU was 14.5 ± 29.5 days, and the mean ± SE hospital postoperative stay was 36.3 ± 37.9 days.

Frequency, risk factors, and outcomes

Thirteen patients matched the diagnostic criteria for VAP, 6 of whom were boys and 7 were girls. The incidence was 21.6 episodes per 1000 mechanical ventilation days. Twelve patients with complex CHD and 1 patient with simple CHD developed at least 1 episode of VAP after cardiac surgery. Ten patients (77%) had cyanotic CHD. Five patients (38%) who developed VAP died during their hospital admission. Table 2 shows the preoperative and postoperative risk factors for development of VAP, and Table 3 shows

Table 1. Congenital heart disease in 100 pediatric patients with and without ventilator-associated pneumonia after cardiac surgery.

Congenital heart disease	Ventilator-associated pneumonia (n = 13) No. (%)	No ventilator-associated pneumonia (n = 87) No. (%)	Total
Complex			
Fallot's tetralogy[a]	3 (23.0)	20 (23.0)	23
Total anomalous pulmonary venous return[a]	0 (0)	1 (1.1)	1
Interrupted aortic arch with pulmonary stenosis	0 (0)	2 (2.2)	2
Dextrotransposition of great arteries[a]	0 (0)	6 (6.8)	6
Levotransposition of great arteries, ventricular septal defect, pulmonary stenosis	0 (0)	3 (3.4)	3
Double outlet of right ventricle[a]	2 (15.0)	5 (5.7)	7
Coarctation of aorta	1 (7.7)	4 (4.6)	5
Hypoplastic left heart syndrome[a]	2 (15.0)	2 (2.3)	4
Pulmonary atresia with intact ventricular septum[a]	2 (15.0)	1 (1.1)	3
Single ventricle with pulmonary atresia[a]	1 (7.7)	2 (2.2)	3
Coarctation of aorta, aortic stenosis, mitral regurgitation	0 (0)	5 (5.7)	5
Tricuspid atresia[a]	1 (7.7)	2 (2.3)	3
Simple			
Atrial septal defect, pulmonary hypertension	0 (0)	8 (9.1)	8
Ventricular septal defect, congestive heart failure	0 (0)	25 (28.7)	25
Partial endocardial cushing defect	0 (0)	1 (1.1)	1
Patent ductus arteriosus	1 (7.7)	0 (0)	1

[a]Cyanotic heart disease.

Table 2. Risk factors for ventilator-associated pneumonia.

Variable	Ventilator-associated pneumonia (n = 13) No. (%)	No ventilator-associated pneumonia (n = 87) No. (%)	Odds ratio (95% confidence interval)	*p*
Age (years; mean ± SD)	0.68 ± 0.96	4.14 ± 5.84		0.001
Sex				0.029
Boys	7 (53.8)	45 (51.7)	1.089 (0.338-3.504)	0.886
Girls	6 (46.2)	42 (48.3)	1.0	
Type of congenital heart disease				
Simple	1 (7.7)	34 (39.1)	1.0	
Complex	12 (92.3)	53 (60.9)	7.698 (0.957-61.926)	0.030
Cyanotic	9 (69.2)	45 (51.7)	1.0	
Acyanotic	4 (30.8)	42 (48.3)	2.41 (0.690-8.419)	0.159
Postoperative days in intensive care unit (mean ± SE)	13.77 ± 4.71	6.34 ± 0.91		0.185[a]
<7	7 (53.8)	59 (71.1)	1.0	
≥7	6 (46.2)	24 (28.9)	2.107 (0.642-6.921)	0.212
Cardiopulmonary bypass time (min; mean ± SD)	142.7 ± 93.00	84.78 ± 56.08		0.047
<120	6 (46.2)	65 (74.7)	1.0	
≥120	7 (53.8)	22 (25.3)	3.447 (1.046-11.342)	0.034
Duration of ventilation (days; mean ± SE)	26.92 ± 8.55	2.95 ± 0.41		0.001[a]
<5	3 (23.1)	65 (74.7)	1.0	
≥5	10 (76.9)	22 (25.9)	9.565 (2.413-37.705)	0.001
Chest tube drainage (days; mean ± SD)	8.62 ± 5.74	5.15 ± 3.88		0.055
<5	4 (30.7)	52 (59.7)	1.0	
≥5	9 (69.2)	35 (40.2)	3.309 (0.943-11.616)	0.052
Central venous catheter (days; mean ± SE)	18.92 ± 3.33	4.98 ± 0.36		0.001[a]
<7	2 (15.38)	67 (77.1)	1.0	
≥7	11 (84.6)	20 (22.9)	18.425 (3.768-90.103)	0.001
Diaphragm paralysis				
Present	11 (84.6)	84 (96.5)	1.0	
Absent	2 (15.38)	3 (3.4)	5.091 (0.764-33.914)	0.065

[a]Mann-Whitney *U* test.

Abbreviations: SD = standard deviation; SE = standard error.

the relationship between VAP, duration of stay in the PICU, duration of hospital stay, and deaths. The development of VAP increased the duration of PICU stay ($p < 0.006$) and hospital stay ($p < 0.001$), and had a direct impact on mortality ($p < 0.001$) [Table 3]. Multivariate analysis showed the following 2 significant independent risk factors for VAP: prolonged use of mechanical ventilation (adjusted odds ratio [AOR], 15.196; 95% CI, 2.158-107.200) and central venous catheter (AOR, 7.342; 95% CI, 1.054-51.140) [Table 4].

Distribution of pathogens

Twenty pathogenic microbial strains were isolated from endotracheal aspirates of 13 patients with VAP. The distribution of microorganisms associated with VAP is shown in Table 5. Gram-negative bacteria were the most prevalent pathogens (14 isolates; 70%) followed by Gram-positive bacteria (5 isolates; 25%) and yeast (1 isolate; 5%). Among the Gram-negative bacteria, there were 3 MDR *P. aeruginosa* and 1 extended-spectrum β-lactamase (ESBL)–resistant *Escherichia coli*.

Mortality

Five patients who developed VAP after cardiac surgery died. Three patients had MDR *P. aeruginosa* cultured from endotracheal aspiration — 1 patient also had *Chryseobacterium meningosepticum*, 1 also had methicillin-resistant *Staphylococcus aureus* (MRSA), and 1 had ESBL *E. coli*. One patient had *P. aeruginosa* and MRSA, and 1 patient had *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *Candida albicans*.

Chi-squared test did not identify any significant factors for mortality after development of VAP.

Table 3. Outcomes after the development of ventilator-associated pneumonia.

Variable	Ventilator-associated pneumonia (n = 13) No. (%)	No ventilator-associated pneumonia (n = 87) No. (%)	Odds ratio (95% confidence interval)	*p*
Postoperative days in intensive care unit (mean ± SE)	63.15 ± 4.715	7.21 ± 0.912		0.006[a]
<7	2 (15.4)	57 (65.5)	1.0	
≥7	11 (84.6)	30 (34.5)	10.45 (2.174-50.327)	0.001
Hospital stay (days; mean ± SE)	110.46 ± 14.086	25.23 ± 1.971		0.001[a]
<45	1 (7.7)	79 (90.8)	1.0	
≥45	12 (92.3)	8 (9.2)	118.5 (13.58-1033.4)	0.001
Mortality				
Survived	8 (61.5)	83 (95.4)	1.0	
Died	5 (38.5)	4 (9.2)	12.969 (2.889-58.221)	0.001

[a]Mann-Whitney *U* test.

Abbreviation: SE = standard error.

Table 4. Multiple logistic regression analysis of independent factors associated with ventilator-associated pneumonia.

Risk factor	Adjusted odds ratio (95% confidence interval)	*p*
Cardiopulmonary bypass time	4.220 (0.865-20.580)	0.075
Duration of ventilation	15.196 (2.158-107.200)	0.006
Duration of chest tube drainage	0.424 (0.058-3.074)	0.396
Duration of central venous catheter	7.342 (1.054-51.140)	0.044

Table 5. Microorganisms isolated from endotracheal aspirate of patients with ventilator-associated pneumonia.

Microorganism	No. of isolates (%)
Pseudomonas aeruginosa	9 (45)
Methicillin-resistant *Staphylococcus aureus*	3 (15)
Methicillin-sensitive *S. aureus*	2 (10)
Stenotrophomonas maltophilia	2 (10)
Extended-spectrum β-lactamase–producing *Escherichia coli*	1 (5)
Klebsiella pneumoniae	1 (5)
Chryseobacterium meningosepticum	1 (5)
Candida albicans	1 (5)

Discussion

VAP is one of the most common nosocomial infections in critically ill pediatric patients. Recent studies have shown a frequency of VAP in infants after open-heart surgery of 21% and an incidence of 6 to 11/1000 mechanical ventilation days for all patients in the ICU [6,13]. This study was retrospective and showed that 13% of children who underwent major heart surgery had at least 1 episode of VAP, with an incidence of 21.6/1000 mechanical ventilation days. Sex, type of CHD (cyanotic or acyanotic), and diaphragm paralysis did not significantly influence the VAP rate in this study. Some authors have found that the development of VAP was closely associated with severity of the underlying disease [11]. This study found that complex CHD was highly associated with VAP after surgery and all patients had the late-onset type, with prolonged mechanical ventilation being the primary cause. Most of the patients who developed VAP were infants (85%). The lack of the endotracheal tube cuff for infants provides an easy passage for oropharyngeal contents to enter the airway. However, patients with complex and cyanotic heart disorders require prompt surgical intervention (i.e., during infancy) for survival to be possible.

Immunodeficiency, immunosuppression, neuromuscular blockade, genetic syndromes, reintubation, and transport to the PICU have been identified as risk factors for development of VAP in some reports [2,6]. This study found that duration of chest tube drainage and cardiopulmonary bypass time were not

risk factors for the development of VAP, but prolonged use of mechanical ventilation and prolonged central venous catheter use were independent and modifiable risk factors. Tjallie et al reported that VAP was significantly associated with bloodstream infection caused by a central venous catheter ($p < 0.01$) [14]. Giard et al found that the prolonged use of a central venous catheter was associated with the development of VAP, particularly for the late-onset type [15]. Some reports have shown that VAP after cardiac surgery causes significantly prolonged PICU and hospital stay [2] and this study confirmed this finding [2].

Nine patients in this study died. Underlying disease severity may contribute to mortality. The population of this study was exclusively infants and children who underwent major heart surgery for CHD, most whom had complex CHD. With the advent of new techniques for the management of pediatric simple CHD, there is less need for these patients to have invasive heart surgery. Most patients who died were younger than 1 year, because infants with complex CHD needed prompt corrective surgery. Patients who developed VAP had a 38.4% mortality rate. Although no risk factors were found after calculation with the chi-squared test, a larger study population was needed for analysis. The patients with VAP who died had resistant strains cultured from endotracheal aspirate, some of which were multidrug resistant, and all patients had polymicrobial infection.

P. aeruginosa and MRSA were the main pathogens in this study, followed by other Gram-negative bacilli and *C. albicans*. Nearly 40% of pathogens were resistant strains. All patients with VAP had late-onset infection. Some authors have documented that the pathogens isolated from endotracheal aspirate of patients who have been intubated for more than 5 days are MRSA, methicillin-sensitive *S. aureus*, *P. aeruginosa*, *Enterobacter* spp., *Klebsiella pneumoniae*, *E. coli*, *Acinetobacter baumannii*, *S. maltophilia,* and yeast [16]. The frequency of MDR pathogens is high [16]. Due to the increase in MDR pathogens, clinicians should prescribe combination therapy for MDR strains and *P. aeruginosa.* The appropriate initial empirical therapy given at the correct dose can improve patients' outcomes and is protective against mortality for patients with VAP. Unnecessary use of antibiotics prior to the appearance of VAP also leads to an increase in morbidity and mortality [17,18]. Soo et al [17] and Bouza et al [7] reported that *P. aeruginosa*, Gram-negative enteric bacilli, and *S. aureus* are the 3 leading causes of VAP, and this was confirmed in this study. Leal-Noval et al have demonstrated that resistant and polymicrobial infection in patients in the ICU is life threatening [19]. According to the American Thoracic Society/Infectious Diseases Society of America guidelines, indiscriminate use of broad-spectrum antibiotics, prolonged hospital admission, and immunosuppressive diseases and therapy are risk factors for the development of infection by resistant pathogens [8]. The 5 patients who died after the development of VAP in this study all had *P. aeruginosa*–associated VAP (3 had MDR *P. aeruginosa*) and all were coinfected with other resistant pathogens. All 5 patients received broad-spectrum antibiotics before the development of VAP and had prolonged hospital admission.

In conclusion, this study found an incidence of 13% for postoperative VAP after congenital heart surgery. Shortening the duration of mechanical ventilation and central venous catheter placement are critical for reducing the risk for VAP, and both measures can significantly decrease the postoperative duration of stay in the ICU and the hospital. Infants with complex CHD are most likely to develop VAP after cardiac surgery and physicians should be alert to the resistant pathogens that have emerged recently in PICUs.

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