INCIDENCE, RISK FACTORS, AND NOSOCOMIAL GERMS FOR VENTILATOR-ASSOCIATED PNEUMONIA IN CHILDREN

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Abstract

Introduction. Early diagnosis and aggressive treatment is fundamental in the management of patients with ventilator-associated pneumonia (VAP).

Aim. The aim of this study was to determine the incidence of VAP among mechanically ventilated children and to identify the main risk factors and nosocomial germs for development of VAP in a critically ill PICU population.

Material and methods. A retrospective, observational study was conducted over a period of 2 years (January 2011 – December 2012) in the Fist Pediatric Intensive Care Unit (PICU) of Emergency Hospital for Children "Louis Turcanu" Timisoara and included all mechanically ventilated children ≥ 48 hours aged 0-18 years.

Results. Of all 51 mechanically ventilated patients, who met the inclusion criteria, 43.13% developed VAP. Patients with VAP needed a greater number of days of mechanical ventilation (mean 23.59 vs. 5.68 days) and a longer duration of hospitalization (mean 42.18 vs. 20.27 days) than those without VAP. Multiple regression analysis identified 4 factors associated with VAP ($p < 0.05$): previously use of an antibiotic (t-statistics (t-stat) = 2.33, $p = 0.036$), previously use of more than one antibiotic (t-stat = 2.89, $p < 0.01$), previously use of an antifungal drug (t-stat = 2.00, $p = 0.05$), and reintubation (t-stat = 2.71, $p < 0.01$). Organisms identified by culture, involved in the etiology of VAP were: gram-negative bacteria 88.8%, fungi 6.6%, and gram-positive bacteria 4.4%.

Conclusions. The incidence of VAP was higher (43%) in our study. Children on previously use of antibiotics or antifungal drugs, or experienced reintubation, developed VAP and had a longer period of mechanical ventilation and hospitalization. Pseudomonas aeruginosa was the most common Gram-negative bacteria associated with VAP.

Keywords: mechanical ventilation, children, ventilator-associated pneumonia

Introduction

VAP is defined as nosocomial pneumonia diagnosed in patients mechanically ventilated for ≥ 48 hours with signs of a new lower respiratory tract infection (1). For a correct and quick VAP diagnosis, medical staff must have a high clinical suspicion combined with blood tests, radiographic examination, and microbiologic analysis of tracheal secretions. Despite advances in supportive care, antimicrobial therapies, mechanical ventilation, and prevention of VAP, it remains an important cause of hospital morbidity and mortality (2).

The epidemiology, associated risk factors, and outcomes of VAP are not as well documented in pediatric patients as they are in adult patients. In adults, the reported incidence of VAP worldwide ranges from 8% to 28% (2,3). The most common organisms isolated from endotracheal aspirate in adult patients who developed VAP were Pseudomonas aeruginosa, Methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae and Acinetobacter baumannii (4,5). In adults, independent risk factors for development of VAP include duration of mechanical ventilation, the presence of chronic pulmonary disease, sepsis, acute respiratory distress syndrome (ARDS), neurological disease, trauma, patient age, previous antibiotic treatment, reintubation, transport out of the Intensive Care Unit (ICU), transfusions and use of histamine-2 blockers (3,6). In addition, VAP in adults has been associated with prolonged duration of mechanical ventilation as well as increased length of ICU stay, hospital stay, hospital cost, and absolute mortality (3).

The incidence of VAP depends on the population studied, the type of ICU, local infections and resistance patterns, and the diagnostic criteria used. Knowledge of the incidence of nosocomial infections and their associated risk factors may be important to allow more effective development and use of preventive measures (7).

PICU patients not only encompass a wide range of ages different from adult ICU patients but also differ in their developmental physiology, underlying disorders, and treatment needs.

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CPIS points	0	1	2
Temperature, ^{0}C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leukocyte count, /mm^3	≥ 4.000 and ≤ 11.000	< 4.000 or > 11.000	< 4.000 or > 11.000 + band forms ≥ 500
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
PaO_2/FiO_2, mmHg	> 240 or ARDS*		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

Table 1. The Clinical Pulmonary Infection Score (CPIS)

We performed this study to determine the incidence of VAP among mechanically ventilated children and to identify the main risk factors and nosocomial germs for VAP in a critically ill PICU population.

Material and methods

A retrospective, observational study was conducted over a period of 2 years (January 2011 – December 2012) in the Fist Pediatric Intensive Care Unit (PICU) of Emergency Hospital for Children "Louis Turcanu" Timisoara and included all mechanically ventilated children ≥ 48 hours, aged 0-18 years.

The following data were collected from each patient: age, sex, admission diagnosis, concomitant chronic diseases, number of days on ventilator, hospital length of stay, outcome (discharge, transfer, death).

All potential risk factors were noted: use of medications (antibiotics, antifungal drugs, steroids, continuous inotrope or vasoactive infusions, histamine type-2 receptor blockers or proton-pump inhibitors, metoclopramide, infusions of benzodiazepines or opiates), route of mechanical ventilation (nasotracheal, orotracheal, or tracheostomy), ventilation tube characteristic (cuffed versus uncuffed tube or tracheostomy), suction system (opened or closed), procedures like need for reintubation

All episodes of VAP were evaluated. VAP was define according to the Clinical Pulmonary Infection Score (CPIS), using 6 parameters (8): body temperature, white blood cells count, volume and appearance of tracheal secretions, oxygenation (PaO2/FiO2 ratio), chest X-ray, and "blind" tracheal aspirate cultures (Table 1). A score > 6 was suggestive for VAP diagnosis. The tracheal aspirates for culture were obtained under aseptic conditions using a "blind" opened suction after detaching the ventilator's tube from the endotracheal tube. The selected germs and the antibiogram from tracheal aspirate culture were also noted.

Preterm babies, patients with congenital immunodeficiency disorders or surgical diseases were excluded from the study. A patient could be included twice when two successive episodes of VAP occurred at least 7 days apart. Patients with positive endotracheal cultures who met the study definition for VAP were considered to have VAP; those who had no clinical signs and symptoms of pulmonary infection were considered to have endotracheal colonization.

This study was approved by the Hospital institutional review board.

Statistical analysis was performed using Microsoft Excel 2007 software. Results are expressed as mean ± SD. Univariate analysis was used to compare the variables for the outcome groups of interest (patients with VAP vs. patients without VAP). Comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using Student's t test for normally distributed variables. All p values < 0.05 were considered statistically significant. Results of the multiple regression analyses are reported as t-statistics with 95% confidence intervals.

Results

Of all 56 mechanical ventilated patients, 51 met the inclusion criteria. Twenty-two (43%) of them developed VAP. Six patients had more than one episode of VAP: 4 of them developed 2 successive episodes, at least 7 days apart, one patient had 3 episodes and other patient had 4 episodes of VAP, resulting in a total of 31 episodes of VAP. Demographic data for patients with VAP and without VAP are shown in Table 2. Of the 51 patients, 37 (72.5%) were males and median age was 2.2 years (26.45 month). In both groups, there were no statistically significant differences in age (p=0.54) or gender (p=0.23). Univariate analysis of admission diagnosis and concomitant chronic diseases were also not statistically significant different between those who developed VAP and those who did not. Instead, the absence of a chronic disease was found to be significant in patients who did not developed VAP (p=0.03). The most common admission diagnosis in both groups was acute respiratory failure and the most frequent concomitant disease was chronic neurological pathology (e.g. cerebral palsy). The cause of ICU admission did not correspond to the incidence of VAP in our study.

All tubes used for intubation were cuffed (Microcuff) and all suction systems were closed, both in patients with or without VAP. We did not found any differences between the intubation route (oral, nasal, or tracheostomy) and the occurrence of VAP.

The duration of mechanical ventilation was longer among patients who developed VAP (23.59±19.03 days vs. 5.68±2.37 days, p<0.01) and also the hospital stay was longer in patients with VAP (42.18±29.83 days vs. 20.27±11.51 days, p<0.01). In this study the mortality rate of patients with VAP was 22.8%. There was no significant difference in mortality between patients with VAP and those without VAP (22.8% vs. 27.5%, p=0.69).

	Non-VAP (n=29)	VAP (n=22)	p
Age (mean ±SD) month (0-216)	30.08±52.30	21.68±44.83	0.54
Sex (n, %)			0.23
Male	23 (79.3)	14 (63.6)	
Female	6 (20.7)	8 (36.4)	
Cause of ICU admission (n, %)			
Acute respiratory failure	19 (65.5)	14 (63.6)	0.89
Neurological disease	2 (6.9)	1 (4.5)	0.72
Cardiovascular disease	3 (10.3)	1 (4.5)	0.43
Severe sepsis	3 (10.3)	5 (22.8)	0.25
Others	2 (6.9)	1 (4.5)	0.72
Concomitant diseases (n, %)			
Chronic respiratory failure	1 (3.4)	4 (18.2)	0.11
Chronic neurological disease	9 (31.0)	9 (40.9)	0.47
Chronic cardiovascular disease	2 (6.9)	1 (4.5)	0.72
Malnutrition	4 (13.8)	4 (18.2)	0.68
Without chronic diseases	13 (44.8)	4 (18.2)	*0.03*
Intubation characteristics (n, %)			
Orotracheal	21 (72.4)	12 (54.5)	0.20
Nasotracheal	6 (20.6)	8 (36.4)	0.23
Tracheostomy	2 (6.9)	2 (9.1)	0.78
Endotracheal tube type (n, %)			-
Cuffed	29 (100)	22 (100)	
Uncuffed	0 (0)	0 (0)	
Suction system (n, %)			-
Closed	29 (100)	22 (100)	
Opened	0 (0)	0 (0)	
Reintubation (n, %)	1 (3.4)	7 (31.8)	*0.01*
Ventilator days (mean ±SD)	5.68±2.37	23.59±19.03	*<0.01*
Hospital length of stay (mean ±SD)	20.27±11.51	42.18±29.83	*<0.01*
Outcome			
Discharged	20 (6.8)	15 (68.1)	0.95
Death	8 (27.5)	5 (22.8)	0.69
Transferred to another hospital	1 (3.4)	2 (9.1)	0.43
Ventilator-associated pneumonia (n, %)			
1 episode only	-	16 (72.7)	-
>1 episode	-	6 (27.3)	-

Table 2. Study Population Characteristics (n=51)

Variables	Coefficients	Standard Error	t-stat	p
Antibiotics	0.35	0.15	2.33	*0.02*
Antibiotics in association	0.58	0.20	2.89	*0.005*
Antifungal drugs	0.27	0.13	2.00	*0.05*
Reintubation	0.45	0.16	2.71	*0.009*

Table 3. Variables associated with VAP, by multiple regression analysis

Variables	Coefficients	Standard Error	t-stat	p
Transfusions	-0.20	0.18	-1.05	0.29
Immunoglobulins	-0.06	0.15	-0.39	0.69
Benzodiazepines	-0.32	0.16	-1.92	0.06
Opiates	0.15	0.14	1.03	0.30
Inotrope infusions	0.08	0.17	0.50	0.61
Steroids	0.07	0.16	0.42	0.67
Metoclopramide	-0.01	0.16	-0.10	0.91
Proton-pump inhibitors	-0.15	0.14	-1.03	0.30

Table 4. Variables not significantly associated with VAP, by multiple regression analysis

	Median	Standard Deviation (SD)
CPIS score	8.16	0.68
Body temperature, ^{0}C	38.2	0.79
Leukocyte count, x10^3/mm^3	18.43	9.24
PaO_2/FiO_2 ratio, mmHg	242.45	107.82

Table 5. Numeric variables of CPIS

Pathogen	n, %
Total	**45 (100)**
Gram-negative bacteria	**40 (88.8)**
Pseudomonas aeruginosa	26 (57.7)
Klebsiella pneumoniae	8 (17.7)
Acinetobacter baumannii	3 (6.6)
Serratia marcescens	3 (6.6)
Gram-positive bacteria	**2 (4.4)**
Staphylococcus aureus MRSA	2 (4.4)
Fungi	**3 (6.6)**
Candida ssp.	3 (6.6)
Polymicrobial	**7 (15.5)**

Table 6. Microorganisms isolated from 31 episodes of VAP

Medium VAP score, according to CPIS was 8.16 (min.= 7 and max.= 9). Means and standard deviations of numeric variables of VAP score (body temperature, leukocyte count, PaO2/FiO2 ratio) are shown in Table 5.

In our study we found that the risk factors for VAP were: previously use of one (p=0.02) or more antibiotics (p<0.01), previously use of an antifungal drug (p=0.05) and reintubation (p<0.01) (Table 3). We did not find any significant differences in the occurrence of VAP and use of transfusions, immunoglobulins, continuous infusion of benzodiazepines or opiates, inotrope infusions, steroids, metoclopramide, and proton-pump inhibitors (Table 4).

Most cases of VAP were caused by Pseudomonas aeruginosa, which accounted for 88.8% of causative organisms (Table 6). Microorganisms isolated in the tracheal aspirates of patients with VAP were P. aeruginosa (n=26, 57.7%), Klebsiella pneumoniae (n=8, 17.7%), Acinetobacter baumanii (n=3, 6.6%), Serratia marcescens (n=3, 6.6%), Staphylococcus aureus MRSA (n=2, 4.4%), and Candida ssp. (n=3, 6.6%). VAP was polymicrobial in 7 patients (15.5%).

Discussions

We conducted a retrospective, observational study to find the incidence, risk factors, and nosocomial germs for ventilator-associated pneumonia (VAP) in mechanically ventilated pediatric patients. Our study population included patients from PICU in an urban pediatric hospital. In the absence of a true gold standard for VAP in children, VAP was defined according to the CPIS, using clinical and biological parameters. CPIS has been used in multiple studies on VAP in adults (9-12), but limited data is available on pediatric patients (13-15). In patients with confirmed VAP, we found a median CPIS score of 8.16, comparable with the values reported in literature (15).

The incidence of VAP among mechanically ventilated children was 43.13%, higher than reported (2,3), but comparable to studies conducted in developing countries (16,17). This can be a reflection of health care of patients.

Like other studies before, our multivariate analysis of risk factors revealed previous use of one ore more antibiotics (p=0.02, respectively p<0.01), antifungal drugs (p=0.05) and reintubation (<0.01) to be positively associated

with the development of VAP (18,19). Aggressive usage of antibiotics and routine periodic change of endotracheal tube should be discouraged.

Several risk factors for the development of VAP identified by other studies such as transfusions, immunoglobulins, narcotics, inotrope infusions, use of gastric stress ulcer prophylaxis were not found to be associated with VAP in our study. This may be due to the fact that we analyzed risk factors temporally related, in the 72-hour period, before a positive endotracheal tube culture and not simply at any time during mechanical ventilation.

Transfusions of different blood products were reported by other studies as risk factors for VAP (20-22). In our PICU, we limit the use of transfusions and immunoglobulins only to patients with sepsis/severe sepsis, and maybe because of the small number of these patients in our study (3 patients non-VAP and 5 patients with VAP), we did not found any association with the occurrence of VAP.

Some studies have identified use of sedation and neuromuscular blockade, to be independently associated with VAP (23,24). The particular association of narcotics with VAP may indicate that gastrointestinal hypomotility secondary to narcotics may be a mechanism for increased risk of VAP via microaspiration of gastric contents. We found no difference in use of sedative agents between patients who developed VAP versus those without VAP, and this is maybe because we used in all patients cuffed endotracheal tubes, witch prevented microaspirations. Similarly, H2 blockers usage was associated with an increased risk as it can alter the gastric pH, thereby facilitating organism multiplication which, when aspirated, can lead to occurrence of VAP. By contrast, probiotics administration reduced the incidence of ICU-acquired pneumonia (25). In our study, we did not found H2 blockers as risk factors for VAP, and the majority of intubated patients received probiotic treatment (data not shown). Data regarding the usage of H2 blockers are controversial. For example, Gautam et al. (26) found in a new research that the absence of tube feeding and the absence of stress ulcer prophylaxis were independent risk factors for VAP.

Other risk factors published before, both in children and adults, but not identified in our study were gender, admission diagnosis, chronic obstructive pulmonary disease, bronchoscopy, tracheostomy, oropharyngeal colonization, prolonged MV, supine body position, tube thoracostomy, enteral feeding, genetic syndrome, and transport out of the PICU (5,14,18,27,28).

The most common bacterial isolates from endotracheal aspirates were Pseudomonas aeruginosa (57.7%), followed by Klebsiella pneumoniae (7.7%). A small number of patients developed VAP with Staphylococcus aureus (4.4%). Pneumonia in pediatric population is often associated with Pseudomonas aeruginosa and Staphylococcus aureus, according to the National Nosocomial Infections Surveillance (NNIS) in the United States (29) and to the European Multicenter Study Group (30).

We found in our study that VAP did not have a serious impact on mortality ($p=0.69$). We also found that patients who developed VAP had longer duration of mechanical ventilation ($p<0.01$) and longer hospital stay ($p<0.01$) than those who did not, which is consistent with other reports (14,16,18,19,26-28).

Conclusions

The incidence of VAP was higher (43%) in our study. Children on previous use of antibiotics or antifungal drugs, or experienced reintubation developed VAP and had a longer period of mechanical ventilation and hospitalization. Pseudomonas aeruginosa was the most common Gram-negative bacteria associated with VAP. Awareness about the various risk factors will aid in reduction of the morbidity associated with VAP. VAP negatively impacts clinical and economic outcomes in critically ill pediatric patients by prolonging the length of mechanical ventilation and hospital stay and may increase total hospital charges.

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