Ventilator-associated pneumonia in an Italian pediatric intensive care unit: a prospective study

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Background: **This study was undertaken to determine the prevalence, risk factors and outcomes associated with ventilator-associated pneumonia (VAP) in a European pediatric intensive care unit (PICU).**

Methods: **A total of 451 children who had been mechanically ventilated in the PICU for ≥48 hours during a 3-year period were enrolled in this prospective study.**

Results: **In comparison with children without VAP, 30 children (6.6%) who developed VAP had a longer PICU stay (*P*=0.0001) and hospital stay (*P*=0.0001), and a higher mortality rate (*P*=0.04). Logistic regression analysis showed that the need for re-intubation (*P*=0.0001), the presence of tracheostomy (*P*=0.04), and enteral feeding (*P*=0.02) were independent risk factors for VAP.**

Conclusions: **A relevant proportion of intubated children develop VAP, which is closely related to invasive procedures. As VAP is associated with increased medical costs and death, multicenter studies are urgently needed to improve the therapeutic approach to VAP and VAP prevention.**

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Introduction

Ventilator-associated pneumonia (VAP) is an important problem in pediatric intensive care units (PICUs) and has a prevalence ranging from 5% to 32%.[1,2] Data collected in the United States show that VAP is the second most common cause of nosocomial infections in PICU patients, accounting for 23% of all infections.[3] Published data suggested that it is associated with a longer PICU stay and a possibly higher mortality rate.[1,4,5] Despite the frequency and severity of this complication, there are few studies on pediatric VAP and these are often difficult to compare because of the lack of a standardized diagnostic approach, and the heterogeneity of the underlying diseases, types of treatment, ages and sample sizes. The aim of this prospective study was to determine the prevalence, risk factors and outcomes associated with VAP in a European PICU.

Methods

The study involved prospectively all of the children aged less than 14 years who were mechanically ventilated in our PICU for ≥48 hours between January 2007 and December 2010. Our PICU is a six-bed unit in a university hospital in Milan, Italy that admits about 350 patients a year. The study was approved by the Institutional Review Board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and written informed consent was obtained from a parent or legal guardian of all of the participants.

The medical records of each patient (demographics, underlying illness, types of procedures, medication, duration of PICU, hospital stays, and mortality) were collected from an electronic database in order to evaluate patients' characteristics. VAP was defined on the basis of clinical, microbiological and radiologic criteria in relation to patient's age, and diagnosed in the presence of at least one of the manifestations such as new or progressive infiltrate, consolidation, cavitation or pleural effusion on chest radiography, plus at least one episode of fever (>38°C) with no other recognized

cause, leukopenia [<4000 white blood cells (WBC)/mm^3] or leukocytosis (≥12 000 WBC/mm^3), and at least two signs of a new onset of purulent sputum: a change in sputum characteristics, increased respiratory secretions or increased suctioning requirements, new-onset or worsening cough, dyspnea or tachypnea, rales or bronchial breath sounds and worsening gas exchange [i.e. O_2 desaturation (PaO_2/FiO_2 levels of ≤240), increased oxygen requirement, or increased ventilation demand], according to the criteria of the Center for Disease Control and Prevention.[6] In all the patients, respiratory cultures were performed and obtained by means of tracheal aspiration; a threshold of ≥105 colony-forming units (CFUs/mL) was considered significant.

Continuous data were analyzed using a two-sided Student's *t* test, after checking data were normally distributed (based on the Shapiro-Wilk statistics) and a two-sided Wilcoxon's rank-sum test otherwise. Categorical data were analyzed using the contingency table analysis with the Chi-square test or Fisher's exact test, as appropriate. The adjusted odds ratio (OR) of VAP and corresponding 95% confidence interval (CI) were derived using unconditional multiple logistic regression models in terms of sex, age (≤2 years, >2 years), underlying illness (yes/no) and clinical procedures. All tests were two-sided, and a *P* value ≤0.05 was considered statistically significant. Data analyses were conducted using SAS version 9.1 (cary, NC, USA).

Results

Of 1446 children admitted in the PICU, 451 mechanically ventilated children (31.2%) were enrolled during the study period. Their mean age (±standard deviation) was 3.8 (±4.5) years (age range, 0.5-14 years; median age, 4.5 years). Cerebral delay (82/451, 18.2%), chronic lung disease (61/451, 13.5%) and gastrointestinal malformation (55/451, 12.2%) were the most common pre-existing diseases, but 144 children (31.9%) had no chronic underlying disease and were admitted for acute infectious disease (58 children for severe community-acquired pneumonia; 33 for complicated bronchiolitis, 30 for sepsis, 23 for meningitis). In children with chronic underlying disease, 96 (31.3%) were surgical patients who received prophylactic antibiotics. No traumatic patient was enrolled. Central venous catheterization (334/451, 74%) and enteral nutrition through a nasogastric tube (271/451, 60.1%) were the most frequently performed procedures. One hundred and fifteen patients (25.5%) had received non-invasive ventilation trial before intubation. Mean pediatric index of mortality (PIM2)±standard deviation was -2.82±1.37.

Thirty patients (6.6%) developed VAP as defined above. Univariate analysis showed the results of the intubated patients with and without VAP (Table 1). The significant risk factors associated with VAP included previous non-invasive ventilation (*P*=0.0003), re-intubation before VAP diagnosis (*P*=0.0001), enteral feeding (*P*=0.0001), transfusion (*P*=0.01) and the presence of a central line (*P*=0.01). No significant differences were related to the underlying illness. Patients with VAP had a longer PICU (*P*=0.0001) and hospital stay (*P*=0.0001) as well as a higher mortality rate (*P*=0.04), regardless of PIM2.

Table 2 shows the results of a logistic regression analysis adjusted for gender, age, underlying illness and clinical procedures. The multivariate ORs of VAP were 9.46 (95% CI=3.34-26.78) for re-intubation (*P*=0.0001), 4.44 (95% CI=1.01-19.96) for the presence

Table 1. Univariate analysis of intubated children with and without VAP

Variables	Children with VAP, *n*=30 (%)	Children without VAP, *n*=421 (%)	*P* value*
Demographics			
Males	13 (43.3)	250 (59.4)	0.09
Mean age±SD (y)	2.43±4.00	3.90±4.47	0.08
Underlying illness			
No underlying illness	6 (20.0)	138 (32.8)	0.15
Brain damage	9 (30.0)	73 (17.3)	0.08
Chronic lung disease	4 (13.3)	57 (13.5)	1.00
Gastrointestinal malformation	2 (6.7)	53 (12.6)	0.56
Malformative syndrome	3 (10.0)	39 (9.3)	0.75
Renal failure	5 (16.7)	36 (8.6)	0.18
Congenital immunodeficiency	1 (3.3)	13 (3.1)	0.94
Autoimmune disease	0 (0.0)	12 (2.9)	1.00
Clinical procedures			
Previous non-invasive ventilation	16 (53.3)	99 (23.5)	0.0003
Re-intubation	12 (40.0)	16 (3.8)	0.0001
Tracheostomy	4 (13.3)	20 (4.8)	0.07
Parenteral nutrition	9 (30.0)	82 (19.5)	0.17
Enteral nutrition	29 (96.7)	249 (59.1)	0.0001
Dialysis (hemodialysis or peritoneal)	4 (13.3)	20 (4.8)	0.07
Transfusion	4 (13.3)	11 (2.6)	0.01
Central venous catheter	28 (93.3)	306 (72.7)	0.01
Inotropic medication	8 (26.7)	57 (13.5)	0.05
Clinical presentation			
PIM2, mean±SD	-2.76±1.31	-2.93±1.39	0.88
Outcome			
Length of PICU stay, d (mean±SD)	42.53±51.46	7.02±7.86	0.0001
Length of hospital stay, d (mean±SD)	66.40±58.76	21.45±25.02	0.0001
PICU deaths	5 (16.7)	25 (5.9)	0.04

*: categorical data were analyzed using contingency table analysis with the Chi-square test or Fisher's exact test. Continuous data were analyzed using a two-sided Student's *t* test and a two-sided Wilcoxon's rank-sum test. VAP: ventilator-associated pneumonia; PICU: pediatric intensive care unit; PIM2: pediatric mortality index; SD: standard deviation.

Table 2. Logistic regression analysis of the factors associated with VAP

Factors	OR	95% CI	*P* value
Female	1.76	0.72-4.30	0.21
Age >2 y	0.56	0.21-1.48	0.24
Underlying illness	1.58	0.57-4.38	0.38
Previous non-invasive ventilation	1.50	0.60-3.74	0.38
Re-intubation	9.46	3.34-26.78	0.0001
Tracheostomy	4.44	1.01-19.96	0.04
Parenteral nutrition	2.52	0.84-7.58	0.10
Enteral nutrition	13.20	1.53-114.17	0.02
Dialysis (hemodialysis or peritoneal)	0.52	0.08-3.26	0.49
Transfusion	1.96	0.34-11.49	0.45
Central venous catheter	2.37	0.47-11.90	0.29
Inotropic medication	1.11	0.32-3.86	0.87

ORs from unconditional regression models adjusted for sex, age (≤2 years, >2 years), underlying illness (yes/no) and clinical procedures, where appropriate. VAP: ventilator-associated pneumonia; OR: odds ratio; CI: confidence interval.

of tracheostomy (*P*=0.04), and 13.2 (95% CI=1.53-114.17) for enteral feeding.

A total of 33 tracheal aspiration cultures from the 30 VAP patients were micro-organism positive. The most frequently isolated microorganisms were *Staphylococcus aureus* (6/33, 18%) and *Pseudomonas aeruginosa* (5/33, 15%), followed by *Stenotrophomonas maltophilia* (3/33, 9%), fungi (3/33, 9%), *Escherichia coli* (2/33, 6%), *Enterobacter* species (2/33, 6%), and *Klebsiella pneumoniae* (2/33, 6%). None of the VAP patients had negative tracheal cultures and no viral pathogen was found.

Discussion

We prospectively collected data to determine the prevalence, risk factors and outcomes associated with pediatric VAP. Although the frequency of VAP has decreased over the last 20 years as a result of the implementation of preventive strategies, it remains a considerable problem associated with PICU admission and has an incidence ranging from 0.6 to 2.3/1000 ventilator-days, depending on the type of PICU.[4,5] VAP occurred in 6.6% of our cohort of 451 mechanically ventilated children, a prevalence that is much lower than that reported by Srinivasan et al (32% of 58 pediatric patients admitted to their PICU)[2] and Casado et al (10.7% of 336 intubated children).[7] These differences can be attributed to differences in VAP definitions as well as study methods and populations, although a low prevalence is always found in PICUs in which efforts have been made to provide education on preventing nosocomial infections.[5] In our PICU, we have a written protocol for infection (including VAP) prevention, and Health Direction of the Hospital regularly monitors nosocomial infections which occur in the various units and provides educational courses on their prevention.

Previous non-invasive ventilation, re-intubation, enteral feeding, transfusion and the presence of a central line were significant risk factors for VAP, but there was no association with the underlying illness. However, logistic regression analysis showed that enteral feeding and re-intubation before the diagnosis of VAP were determined and that tracheostomy was the only significant independent risk factor. During tracheostomy, we used cuffed endotracheal tubes, and indications for tracheotomy included bypassing airway obstruction, providing access for prolonged mechanical ventilation, and facilitating tracheobronchial toilet. Our findings were partially consistent with those of other studies although the data were difficult to compare because of heterogeneous procedures. Healthcare-associated pneumonia was suggested and VAP was considered as an equivalent. Srinivasan et al[2] identified continuous enteral feeding, narcotic use, female gender and post-surgical admission as independent risk factors for VAP in children. In another prospective surveillance study of 361 subjects, continuous enteral feeding, re-intubation, bronchoscopy and prior use of antibiotics were identified as independent predictors.[8] Many of the studies showed the risk of aspiration and by-passing of airway defences of the patient, thus allowing bacteria to enter the lungs.[6] This indicates that reducing the risk of aspiration and shortening the duration of mechanical ventilation are crucial in reducing the risk of VAP. However, it remains to be clarified why non-invasive ventilation is associated with an increased risk of VAP.

Our data have shown that VAP is associated with prolonged PICU or hospital stay regardless of illness severity,[4,5] and with increased mortality. Univariate analysis by Bigham et al[5] showed a similar increase in mortality in children with VAP although other studies have concluded that VAP is not independently associated with death.[9] However, VAP is thought to be associated with high medical costs,[5,6] and its prevention should be considered a priority in PICU patients.

The most frequently isolated organisms in our study were *Staphyococcus aureus* and *Pseudomonas aeruginosa*, although gram-negative bacteria were more frequently isolated than gram-positive bacteria. These findings are in consistent with those of other studies, and are similar in adult and pediatric series.[2,4]

One limitation of our study is that the culture specimens were obtained by means of endotracheal aspiration, so the results might reflect pathogens colonizing the upper airways. Gauvin et al[10] found that blind bronchoalveolar lavage (BAL) with a

bacterial index of >5 was the most reliable means of diagnozing VAP in a 27-month prospective study of 30 intubated children. However, the risks of invasive methods may rule out the routine use of BAL in critically-ill children. Our cultures were analyzed quantitatively using a high threshold count of bacterial growth in order to improve specificity in distinguishing infection and colonization of the lower airways. Using BAL as the reference standard, Sachdev et al[11] have shown that tracheal aspirates with a threshold value of 10^5 CFUs/mL are sensitive and specific. However, more studies are required to compare different methods of diagnozing VAP and different pediatric therapeutic regimens.

In brief, our findings show that a small but not negligible proportion of intubated children develop VAP, and that this is closely related to invasive procedures. VAP increases PICU and hospital stays and is also a risk factor for death. Broad-spectrum antibiotics should be considered in the initial empiric approach to this severe disease, but more homogeneous studies are needed to define the diagnostic and therapeutic approach to children with suspected VAP and evaluate methods for its prevention.

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Ethical approval: The study was approved by the Institutional Review Board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico. Written informed consent was obtained from the parents or legal guardians of the study participants.
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Contributors: Patria MF was the consultant in pneumology, analyzed the data and wrote the first draft of the manuscript. Chidini G, Ughi L, Prandi E and Montani C visited the patients, collected the data and performed the data entry. Galeone C performed statistical analyses. Calderini E supervised the study and criticallly reviewed the manuscript. Esposito S was the consultant in pediatric infectious diseases, supervised data collectionn and co-wrote the manuscript.

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