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The Clinico-radiologic Evaluation and Risk Factor of Ventilator-associated Pneumonia in a Pediatric Care Unit of a Tertiary Center

Üçüncü Basamak Bir Merkezin Pediatrik Yoğun Bakım Ünitesinde Ventilatörle İlişkili Pnömoninin Risk Faktörleri ve Klinik-radyolojik Değerlendirmesi

Gürkan Atay[1], Emine Çalışkan[2], Nezahat Gürler[3], Demet Demirkol[1], Ayper Somer[4]

[1]İstanbul University İstanbul Faculty of Medicine, Department of Pediatric Intensive Care, İstanbul, Turkey
[2]İstanbul University İstanbul Faculty of Medicine, Department of Pediatric Radiology, İstanbul, Turkey
[3]İstanbul University İstanbul Faculty of Medicine, Department of Microbiology and Clinical Microbiology, İstanbul, Turkey
[4]İstanbul University İstanbul Faculty of Medicine, Department of Pediatric Infectious Diseases, İstanbul, Turkey

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ABSTRACT

Objective: Ventilator-associated pneumonia (VAP) is the second most common form of hospital-acquired infection. Prediction of possible etiologic agents and initiation of appropriate and narrow-spectrum antibiotherapy is crucial to reduce morbidity and mortality. Clinical and radiologic variable analyses may help clinicians to foresee the usual cause of VAP.

Methods: This was a retrospective observational study evaluating the clinico-radiologic characteristics of VAP in a pediatric intensive care unit (PICU) of a tertiary referral university hospital between January 2011 and December 2016.

Results: A total of 1,323 patients in the PICU were followed during the study period, wherein 78 with a median age of 10 months (1-188) were detected to have VAP. Patients were divided into two groups according to the etiologic agents as gram-positive (n=16, 20.5%) and gram-negative VAP (n=62, 79.5%). Radiologic findings included peribronchial thickening (n=32, 41.0%), diffuse interlobular septal thickening (n=38, 48.7%), patchy infiltrate (n=54, 69.2%), consolidation (n=54, 69.2%), and pleural effusion (n=21, 26.9%). The presence of consolidation and pleural effusion were significantly more common among the patients with gram-positive VAP (p-values are 0.004 and 0.02).

Conclusion: Clinical and radiologic evaluation of patients may be a clue for the estimation of the microbiology of VAP, which is highly recommended before the initiation of empirical antibiotherapy.

Keywords: Ventilator-associated pneumonia, pediatric intensive care, clinico-radiologic evaluation

ÖZ

Amaç: Ventilatör ilişkili pnömoni (VİP), hastane kaynaklı enfeksiyonun ikinci en yaygın şeklidir. Olası etiyolojik ajanın öngörülmesi ve uygun, dar spektrumlu antibiyotik tedavisinin başlatılması, morbidite ve mortaliteyi azaltmak için çok önemlidir. Klinik ve radyolojik değişkenlerin analizi, klinisyenlerin VİP'nin olağan şüphesini önceden görmelerine yardımcı olabilir.

Yöntemler: Bu çalışma, Ocak 2011 ile Aralık 2016 arasında üçüncü basamak bir üniversite hastanesinin pediatrik yoğun bakım ünitesinde VİP'nin kliniko-radyolojik özelliklerini değerlendiren retrospektif bir gözlemsel çalışmaydı.

Bulgular: Çalışma süresi boyunca çocuk yoğun bakım ünitesinde 1.323 hastayı takip ettik. Ortanca yaşı 10 ay olan (1-188) 78 hastada VİP tespit edildi. Hastalar etiyolojik etkenlere göre Gram-pozitif (n=16, %20,5) ve Gram-negatif ilişkili VİP (n=62, 79,5). Radyolojik bulgular arasında peribronşiyal kalınlaşma (n=32, %41,0) olmak üzere iki gruba ayrıldı. Diffüz interlobüler septal kalınlaşma (n=38, %48,7), yamalı infiltrat (n=54, %69,2), konsolidasyon (n=54, %69,2) ve plevral efüzyon (n=21, %26,9). Konsolidasyon varlığı ve plevral efüzyon, Gram-pozitif ventilatör ilişkili pnömonisi olan hastalarda anlamlı olarak daha yaygındı (p değerleri; 0,004 ve 0,02).

ORCID IDs of the authors: G.A. 0000-0002-0317-5872; E.Ç. 0000-0001-9869-1396; N.G. 0000-0002-1134-658X; D.D. 0000-0001-9578-9267; A.S. 0000-0002-7827-1113.

Corresponding Author/Sorumlu Yazar: Gürkan Atay,
E-mail: drgurkanatay@yahoo.com

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ÖZ

Sonuç: Hastaların klinik, risk faktörleri ve laboratuvar parametreleriyle birlikte radyolojik olarak değerlendirilmesi VİP'nin olası etkeninin öngörülmesinde fayda sağlayarak, uygun etkene yönelik antibiyoterapinin kısa sürede başlanmasına olanak tanıyabilir.

Anahtar kelimeler: Ventilatör ilişkili pnömoni, pediatrik bakım, kliniko-radyolojik değerlendirme

INTRODUCTION

Ventilator-associated pneumonia (VAP), which is defined as pneumonia occurring >48-72 h of mechanical ventilation (MV) is an important cause of nosocomial mortality (1) and is most common in adults and the second most common form of hospital-acquired infection (HAI) in the bloodstream of pediatric patients (2). The average risk of VAP is reported between 3% and 19% in children, with a cumulative incidence of 1.1-27.1 per 1,000 ventilator days (2-4). Together with VAP attributable mortality, which is nearly 13%, several reports also highlight the VAP-related undesirable outcomes, such as prolonged MV duration and length of hospital stay (LOS), economic burden, and tremendous healthcare work use (5-7).

Another unwanted consequence of increased VAP incidence is the emergence of resistant nosocomial pathogens. These patients require longer durations and several courses of antibiotherapy, thus pre-designed rational policies should be conducted in the facilities. Recent guidelines are recommended to utilize empiric antibiotherapy options of narrow-spectrum and shorter duration therapies to minimize the patient's exposure to unnecessary medicine and decrease antibiotic resistance rates (1). Dual gram-negative and empiric methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic regimens are suggested to be limited and selection should be patient-tailored. Therefore, possible etiologic agent prediction and appropriate initiation of narrow-spectrum antibiotherapy are crucial to reduce morbidity, mortality, and many other VAP-related complications. Clinical and radiologic variable analyses may help clinicians to foresee the usual causes of VAP. As far as we know; a very limited number of studies were reported that particularly investigated the relationship between radiologic characteristics and microbiology of VAP. Children's data are even rarer.

Proceeding from this point of view, the clinico-radiologic characteristics of pediatric patients who were diagnosed with VAP in a referral university hospital were evaluated.

METHODS

Study Design and Hospital Setting

This was a retrospective observational study evaluating the clinico-radiologic characteristics of VAP in a pediatric intensive care unit (PICU) of a tertiary referral university hospital between January 2011 and December 2016. Our PICU is a 6-bed unit, accepting complicated pediatric patients aged 1 month to 18 years old. It has 2, each with 3 patient beds, without an isolation room. The patient-to-nurse ratio is 2:1.

Medical records of patients were retrospectively evaluated using standardized surveys. Information regarding, age, gender, underlying disease, LOS before PICU admission, previous antibiotic use, duration and nature of MV (intubation/tracheostomy), antibacterial therapy regimen and duration, and clinical outcomes were recorded.

Laboratory and Microbiologic Evaluation

Laboratory evaluation included the results of complete blood count, C-reactive protein, and procalcitonin analyses that were ordered throughout the therapy. Microbiological culture reports of tracheal aspirate material (from the endotracheal tube and the tracheostomy cannula) of patients, together with antimicrobial susceptibility results, were recorded.

The tracheal aspirate specimen was initially investigated with gram stain; cultured in 5% sheep blood agar (Becton Dickinson, Germany) and chocolate agar (Oxoid, England) which was incubated in 5% CO_2 atmosphere; and cultured on Mac Conkey agar (Oxoid, England) and incubated in the normal atmosphere for 24-48 h. For anaerobic conditions, the GasPak system (Becton Dickinson, USA) was used. Isolated pathogens were identified with conventional methods (gram stain, catalase, oxidase, DNase, carbohydrate fermentation, urease effect, use of citrate, lysine decarboxylase, Voges Proskauer, motility and indole test, etc.).

Antimicrobial susceptibility was performed, according to the Clinical Laboratory Standards Institute (CLSI) recommendations, in Mueller Hinton agar (Oxoid, England) by the Kirby Bauer disc diffusion method. Minimal inhibitory concentration analysis was performed using E-test (bioMeriéux, France) and results were evaluated according to the CLSI criteria (8).

Definition of Terms

Since January 2010, infection control nurses assigned from the Hospital Infection Control Committee have performed active monthly surveillance of HAIs in PICU, with pediatric infectious disease specialists. VAP diagnosis was performed according to the Center for Disease Control and Prevention definition criteria (9). According to this, at least one of the following should be present: a new or progressive infiltrate; consolidation, cavitation, or pleural effusion evident on chest radiography, with at least one episode of fever (>38 °C) attributable to no other recognized cause; leukopenia [<4,000 white blood cells (WBC)/mm^3] or leukocytosis (≥12,000 WBC/mm^3); and at least two signs of new-onset purulent sputum (a change in sputum characteristics, an increased amount of respiratory secretion or in suctioning requirements, new-onset or worsening cough, dyspnea or tachypnea, rales or

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bronchial breath sounds, or a worsening gas exchange profile (i.e., O_2 desaturation; PaO_2/FiO_2 level ≤240), an increased oxygen requirement, or an increased ventilation need) (10).

VAP incidence was calculated as follows: (number of cases with VAP/total number of patients who received MV x100) = VAP rate per 100 patients.

The terms of the radiologic classification used the glossary of the Fleischner Society for thoracic imaging (11). Peribronchial thickening was defined as thin circular increased density, which was peribronchially observed. Interlobular septal thickening was accepted as affecting one of the components of the septa that might be responsible for the thickening and so render septa visible (Figure 1). Infiltrate was accepted as patchy opacification with undefined borders on chest X-ray and widespread ground glass appearance on computed tomography (CT) (Figure 2). Homogeneous dense lobar-segmental opacification with the air bronchogram and loss of silhouette sign on chest X-ray and lobar/segmental increased density on CT was defined as consolidation (Figure 3). Pleural effusion was defined as blunting of the costophrenic or cardiophrenic angle or a meniscus laterally seen and gently sloping medially (Figure 4).

Clinico-radiological characteristics between the gram-positive and gram-negative-related VAP were compared in the end.

Radiologic Evaluation

Radiologic modalities (chest X-ray and/or computerized thorax tomography), which were performed on the day of VAP diagnosis were evaluated by a pediatric radiologist from the hospital computer system. Findings were classified into 5 groups as a peribronchial thickening, interlobular septal thickening, patchy infiltrate (separate patchy opacification with uncertain borders), lobar/segmental consolidation, and pleural effusion.

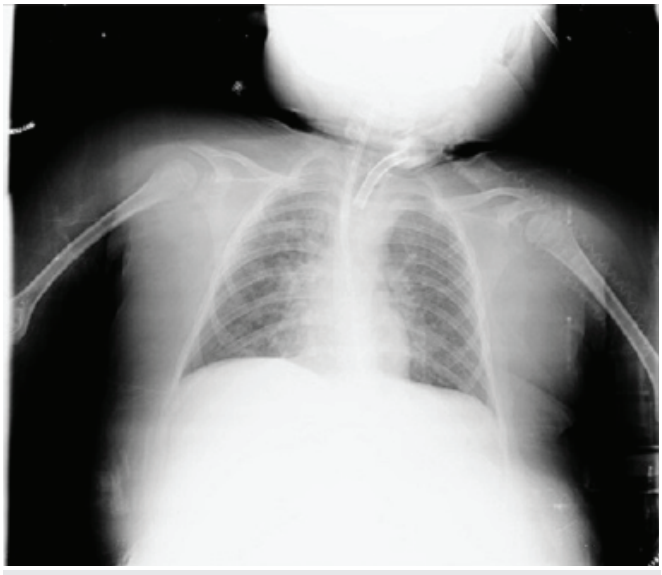

Figure 1. X-ray reveals "diffuse interlobular septal thickening" in both lungs

Statistical Analysis

Statistical analysis of data was performed using the statistical package for social science for Windows version 21.0 (SPSS 21.0, SPSS Inc. USA). Normality was assessed using the Shapiro-Wilk tests and histogram graphics. Data are presented as median,

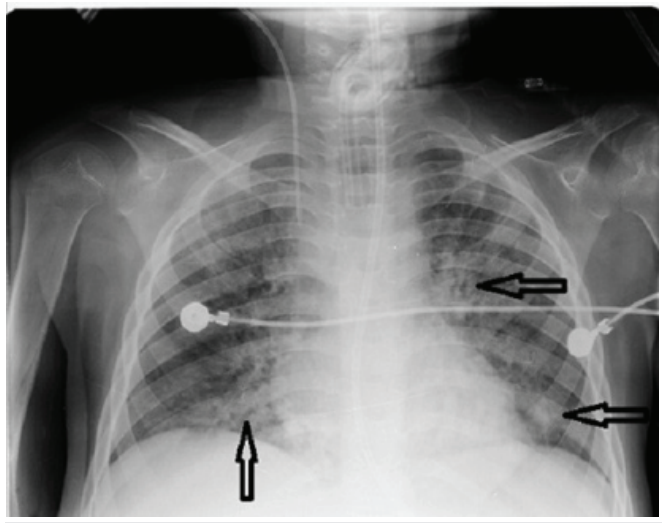

Figure 2. The X-ray revealed the scattered and patchy opacifications with uncertain borders that do not erase the contour of the heart or diaphragm representing an "infiltrate"

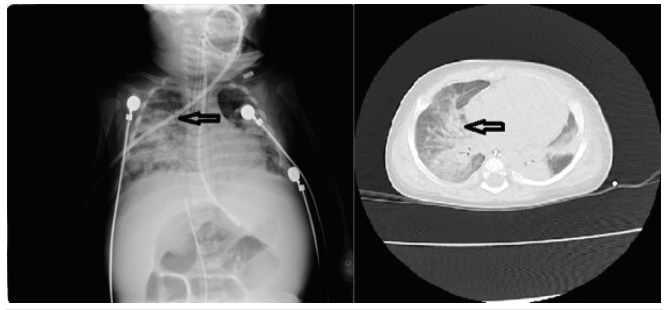

Figure 3. Lobar/segmental consolidations are detected on X-ray (right) and CT (left) of the lungs. Air-bronchograms are seen (arrows)

CT: Computed tomography

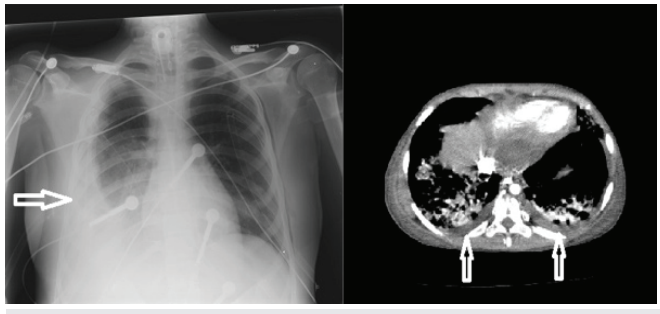

Figure 4. The pleural fluid is demonstrated on X-ray (right) and CT (left) (arrows)

CT: Computed tomography

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minimum, maximum, frequency, and percentage. Categorical variables between the groups were compared with the Pearson χ^2 test or the Fisher exact test when the expected cell size was <5. The Mann-Whitney U test was used for continuous variables, which are not normally distributed. All p-values are based on 2-tailed statistical analyses and a p-value of <0.05 was considered statistically significant. The significant predictors of gram-positive and gram-negative-related VAP with p≤0.05 in univariate analysis were fitted to perform a logistic regression analysis model to identify independent risk factors.

Ethical Committee and Informed Consent

This study was performed with the permission of the İstanbul University İstanbul Faculty of Medicine Clinical Research Ethical Committee (decision no: 772, date: 29.05.2018). This was a retrospective case-control study, thus informed consent was not obtained.

RESULTS

During the study period, a total of 1,323 patients attended to PICU, wherein 78 patients with the median age of 10 months (1-188) were detected to have VAP. Twenty-six patients (33.3%) were female. VAP incidence was 10.3/1,000 ventilator days. Patient characteristics were presented in Table 1.

Table 1. Characteristics of patients

Age [months, median (range)]	**10 (1-188)**
Gender, female, n (%)	26 (33.3)
PRISM score on PICU admission	9 (2-18)
Gram-positive organisms, n (%)	
MRCNS	9 (11.5)
MRSA	4 (5.1)
Streptococcus pneumonia	2 (2.6)
Corynebacterium spp	1 (1.3)
Gram-negative organisms, n (%)	
Pseudomonas aeruginosa	22 (28.2)
Acinetobacter baumannii	22 (28.2)
Kleibsiella pneumonia	6 (7.7)
Escherichia coli	1 (1.3)
Serratia marcescens	2 (2.6)
Stenotrophomonas maltophilia	9 (11.5)
LOS before PICU admission, d, mean ± SD	24 (10-128)
Length of PICU stay before the diagnosis of VAP, d, median (range)	28 (4-188)
Length of MV before the diagnosis of VAP, d, median (range)	14 (2-184)
Clinical outcome	
PICU mortality, n (%)	10 (12.8)
VAP cured	55 (70.6)
Tracheostomies	13 (16.6)

SD: standard deviation, PICU: pediatric intensive care unit, VAP: ventilator-associated pneumonia, MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase-negative *staphylococcus*

The patients were divided into two groups according to etiologic agents as Gram-positive (n=16, 20.5%) and Gram-negative-related VAP (n=62, 79.5%). The most common Gram-positive microorganism was methicillin-resistant coagulase-negative staphylococcus, whereas *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the most common Gram-negative bacteria (n=22, 28.2%). The etiologic distribution of VAP was shown in Table 1.

The most common cause of PICU admission was respiratory-related conditions (n=36, 46.2%), followed by neurologic conditions (n=21, 26.9%), post-operative follow-up (n=11, 14.1%), cardiovascular disorders (n=9, 11.5%), and decompensation of underlying metabolic disease (n=1, 1.3%). When admission diagnostic category was compared between Gram-positive and gram-negative-related VAP, no significant difference was achieved (Table 2).

Underlying chronic illnesses were noted in 59 (75.6%) patients, of which, the most common was chronic neurologic disorder (n=23, 29.5%). Gram-positive-related VAP was significantly more common among patients with chronic cardiovascular disorders (p=0.049). Possible risk factors for the development of VAP were compared between etiologic agents in Table 2. The history of surgery and thorax drainage were significantly more common in the Gram-positive-related VAP group (p-values are 0.038 and 0.026, respectively); whereas the incidence of rectal carbapenem-resistant *Klebsiella pneumonia* (CRKP) colonization was significantly higher in patients with gram-negative-related VAP (p=0.014). Empirical glycopeptide and carbapenem use were significantly higher in patients with gram-negative-related VAP (p-values are <0.001 and 0.001, respectively)

The mean LOS before PICU admission was 24 (10-128) days and the mean length of PICU stay before the diagnosis of VAP was 28 (4-188) days. The length of MV before the diagnosis of VAP was significantly longer among the patients with Gram-negative-related VAP [17 (4-184) days] compared with that of the Gram-positive ones [9 (2-33) days] (p=0.024). No significant difference was achieved in terms of laboratory variables between the two groups (p>0.05) (Table 2).

Radiologic findings included peribronchial thickening (n=32, 41.0%), diffuse interlobular septal thickening (n=38, 48.7%), patchy infiltrate (n=54, 69.2%), consolidation (n=54, 69.2%), and pleural effusion (n=21, 26.9%) (Figures 1-4). The presence of consolidation and pleural effusion were significantly more common among the patients with gram-positive-related VAP (p-values are 0.004 and 0.020, respectively).

A logistic regression analysis including the parameters with a p-value of <0.05 found in the univariate analysis was used. Empirical glycopeptide and carbapenem were found to be independent risk factors for the development of Gram-negative-related VAP, whereas the same applied to the presence of consolidation with Gram-positive-related VAP (Table 3).

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Table-2. Comparison of VAP according to etiologic microorganism

	Gram-positive	Gram-negative	p
Age [months, median (range)]	9 (1-190)	27 (2-157)	0.17
Comorbid conditions, n (%)	10 (62.5)	49 (79)	0.17
Chronic cardiovascular disease	5 (31.3)	7 (11.3)	**0.049**
Neurologic disorder	3 (18.8)	20 (32.3)	0.23
Metabolic disease	1 (6.3)	8 (12.9)	0.45
Chronic respiratory disease	-	2 (3.2)	0.63
Chronic kidney disease	-	5 (8.1)	0.30
Malignancy	-	2 (3.2)	0.63
Chronic liver disease	1 (6.3)	5 (8.1)	0.64
Admission diagnostic category, n (%)			
Respiratory	6 (37.5)	30 (48.4)	0.43
Cardiovascular	2 (12.5)	7 (11.3)	0.59
Neurological	5 (31.3)	16 (25.8)	0.66
Post-operative	3 (18.8)	8 (12.9)	0.40
Metabolic disorder	-	1 (1.6)	0.79
Risk factors			
Tracheostomy	3 (18.8)	5 (8.1)	0.20
Percutaneous endoscopic gastrostomy	1 (6.3)	2 (3.2)	0.50
Immunosuppression	2 (12.5)	5 (8.1)	0.44
Surgery	6 (37.5)	9 (14.5)	**0.038**
Renal replacement therapy	-	4 (6.5)	0.39
Central venous catheterization	15 (93.8)	62 (100)	0,2
Thorax drainage tube	3 (18.8)	1 (1.6)	**0.026**
Total parenteral nutrition	16 (100)	60 (96.8)	0.63
Rectal VRE colonization	4 (25.0)	20 (32.3)	0.40
Rectal CRKP colonization	2 (12.5)	28 (45.2)	**0.014**
Empirical antibiotic use before a diagnosis of VAP, n (%)			
Carbapenems	2 (12.5)	45 (72.6)	**<0.001**
Glycopeptides	9 (56.3)	58 (93.5)	**0.001**
Anti-pseudomonal penicillin	10 (62.5)	51 (82.3)	0.08
Aminoglycosides	11 (68.8)	51 (82.3)	0.19
Linezolid	-	6 (9.7)	0.23
LOS before PICU admission, d, mean ± SD	23 (10-94)	26 (12-128)	0.78
Length of PICU stay before the diagnosis of VAP, d, mean ± SD	24 (4-175)	32 (4-188)	0.44
Length of MV before the diagnosis of VAP, d, mean ± SD	9 (2-33)	17 (4-184)	**0.024**
Laboratory parameter, median (range)			
White blood cell count	14,600 (8,300-15,900)	11,340 (4,600-33,000)	0.99
Neutrophil count	10,000 (4,700-12,400)	7,000 (1,800-16,000)	0.61
Lymphocyte	3,800 (2,100-7,100)	2,050 (650-11,300)	0.98
CRP	307 (69-545)	90 (0.1-259)	0.52
PCT	14.1 (4.7-36)	1.2 (0.23-17.5)	0.27
Radiologic findings			
Peribronchial thickening	5 (31.3)	27 (43.5)	0.37
Diffuse interlobular septal thickening	9 (56.3)	29 (46.8)	0.49
Patchy infiltrate	13 (81.3)	41 (66.1)	0.24
Consolidation	14 (87.5)	30 (48.4)	**0.004**
Pleural effusion	8 (50)	13 (21)	**0.020**

*MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase-negative *staphylococcus*, MV: mechanical ventilation, PICU: pediatric intensive care unit, S: standard deviation, VAP: ventilator-associated pneumonia, CRP: C-reactive protein, PCT: procalcitonin

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Table 3. Multivariate analysis of the risk factors in predicting the VAP etiology

Variable	p	Adjusted OR	95 CI
Carbapenems	0.010	30.6	2.25-416.7
Glycopeptides	0.031	10.7	1.25-93.1
Consolidation	0.045	3.2	1.05-12.3

CI: confidence interval, OR: odds ratio, VAP: ventilator-associated pneumonia

DISCUSSION

The National Healthcare Safety Network reports a steady decline in the VAP incidence in the United States; however, it is not valid for the low and middle-income countries, which range from 8.87 to 18.7/1,000 ventilator days (12-14). The incident reports from our country vary between different centers and between pediatric and adult ICUs. A multicenter study regarding patients in the adult ICU reports VAP incidence as high as 26.5/1,000 days, whereas the National Surveillance report of 2015 estimated a VAP incidence in PICUs as 4.7 patients per 1,000 ventilator days (15,16). A similar incidence was also reported by Şevketoğlu et al. (17) in their PICU study. Our VAP incidence was 10.3/1,000 ventilator days, which may be related to the complexity of our patients and the longer duration of PICU stay.

Most of the national and international reports highlight the dominance of Gram-negative etiology of VAP. Aerobic Gram-negative bacilli like *E. coli, Klebsiella pneumonia, Enterobacter* spp, *Pseudomonas aeruginosa* and *Acinetobacter* spp, and Gram-positive cocci (*S. aureus*, MRSA, and *Streptococcus* spp) constitute the majority of cases, whereas viruses and fungi are exceptional (18,19). The Extended Prevalence of Infection in Intensive Care study reported that 62% of the cases were related to gram-negative microorganisms (20). In our study cohort, consistent with previous reports, the majority of patients (79.4%) had Gram-negative-associated VAP. Empirical glycopeptide and carbapenem use were found to be independent risk factors for Gram-negative-related VAP. Similarly, rectal CRKP colonization incidence was higher among those patients. This may be related to the decomposition of intestinal microbiota, which is also more common in patients with longer PICU stay.

Recent guidelines recommended the initial antimicrobial therapy, including the coverage for *S. aureus, Pseudomonas aeruginosa,* and other gram-negative bacilli (1). MRSA coverage, in the first place, is not recommended unless there is an increased risk for MRSA, such as patients treated in units where the resistance of *S. aureus* isolates is >10-20% or unknown. The golden standard for diagnosis is bacterial growth; however, it requires a specific time, which is extremely important in the pediatric age group. Hopefully, newer molecular techniques will be developed and would be more widely used shortly (21). For all that, traditional methods, such as portable chest radiographs, may help to predict the etiologic agent in the early phase. Conventional radiology was used for the diagnosis of VAP in children for a long time. However, specific definitions, like consolidation or cavity formation, were used for the definition of VAP, other than estimating the etiologic agent.

Several reports defined the radiologic differences between viral and bacterial agents or characteristic imaging findings for specific pathogens (22-24). Okada et al. (22) reported that ground-glass attenuation and bronchial wall thickening on CT were demonstrative for *Pseudomonas aeruginosa*-related pneumonia. Another study of the same facility found that pleural effusion was significantly more frequent in patients with MRSA pneumonia than those with MSSA pneumonia (24). Our literature research in the English language could not reveal any study evaluating the differences between the Gram-positive and negative etiology of VAP. In our study, the presence of pleural effusion and consolidation were higher among the patients with Gram-positive microorganisms, which can be accepted as an important finding since the interpretations were performed by a pediatric radiologist. There is an instructive report, which is pointing the importance of specialist evaluation since opinions between clinicians and radiologists are contradicting, particularly for the discrimination of atelectasis and consolidation (25). Therefore, we highly recommend to the consulate conventional radiographs with a specialist if possible.

The onset of VAP may also be important for the estimation of the etiologic agent. Some investigators found that MSSA was the major bacterium grown in early VAP cases (the cases occurring within 4 days of MV), whereas MRSA and *Acinetobacter baumannii* were the most common bacteria in late VAP, which others declared no specific correlation (26,27).

Compatible with former studies, the median length of MV in our study cohort was significantly more common among the patients with gram-negative-related VAP. In addition, the history of surgery, thorax drainage tube, and presence of chronic cardiovascular disorders were higher in the gram-positive-related VAP group. Therefore, empirical antibiotherapy with broadened gram-positive coverage, including MRSA, may be recommended in cases with formerly specified risk factors.

Study Limitations

Study limitations include the retrospective design of the study, relatively small number of patients and third-level center, high presence of underlying chronic disease, and long hospital stays in patients, which affect the heterogeneity in the study cohort.

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CONCLUSION

In conclusion, clinical and radiologic evaluation of patients may be a clue for the estimation of the microbiology of VAP, which is highly recommended before the initiation of empirical antibiotherapy.

Ethics Committee Approval: This study was performed with the permission of the İstanbul University İstanbul Faculty of Medicine Clinical Research Ethical Committee (decision no: 772, date: 29.05.2018).

Informed Consent: This was a retrospective case-control study, thus informed consent was not obtained.

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Conflict of Interest: No conflict of interest was declared by the authors.

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Etik Komite Onayı: Bu çalışma İstanbul Üniversitesi İstanbul Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'nun (karar no: 772, tarih: 29.05.2018) izni ile gerçekleştirilmiştir.

Hasta Onayı: Bu retrospektif bir olgu kontrol çalışmasıydı, bu nedenle bilgilendirilmiş onam alınmadı.

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