Evaluation of Microorganisms Causing Ventilator-Associated Pneumonia in a Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Ventilatör İlişkili Pnömoniye Neden Olan Mikroorganizmaların Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to identify microorganisms causing ventilator-associated pneumonia (VAP) and also study the antibiotic resistance/susceptibility.

Materials and Methods: We retrospectively assessed microorganisms isolated from patients diagnosed with VAP in a pediatric intensive care unit between January 1, 2014, and June 30, 2016.

Results: We included 44 patients diagnosed with VAP. The prevalence thereof was 8.6 patients per 1,000 ventilator days. Mechanical ventilation was required for 56.5% of patients. Thirty-three patients (75%) died. An underlying chronic disease was detected in 75% of patients (n=33). Fifty microorganisms were isolated from 44 patients. Single microorganisms were isolated from 86.4% (n=38) and two from 13.6% (n=6) of patients. Of all the isolated bacteria, 96% (n=48) were gram-negative; the most common was *Pseudomonas aeruginosa* (32%), followed by *Klebsiella pneumoniae* (24%) and *Acinetobacter baumannii* (22%). The isolates were most susceptible to colistin (92.6%), followed by piperacillin-tazobactam (71.4%), amikacin (65.2%), and gentamicin (52.2%). No enterobacterium or *Acinetobacter* strain was resistant to colistin; however, 13% of *P. aeruginosa* isolates were resistant.

Conclusion: In VAP, it is essential to catalog antibiotic resistance patterns of bacteria present in the unit to ensure that empirical antibiotic therapy is effective.

Keywords: Ventilator-associated pneumonia, pediatric intensive care, microorganism, antibiotic

ÖZ

Amaç: Bu çalışmanın amacı ventilatör ilişkili pnömoniye (VIP) neden olan mikroorganizmaların belirlenmesidir. Ayrıca antibiyotik duyarlılık ve direnç oranları belirlenmiştir.

Gereç ve Yöntem: Çocuk yoğun bakım ünitesinde, 1 Ocak 2014-30 Haziran 2016 tarihleri arasında VİP tanısı alan hastalar retrospektif olarak değerlendirilmiştir.

Bulgular: Çalışmaya VİP tanısı alan 44 hasta alındı. VİP hızı 1000 ventilatör gününde 8,6 olarak saptandı. Mekanik ventilatör kullanım oranı %56,5 idi. VİP tanısı alan olguların %75 (n=33)'nin öldüğü saptandı. VİP tanısı alan hastaların %75 (n=33)'inde altta yatan kronik hastalık tespit edildi. VİP tespit edilen 44 olguda 50 mikroorganizma izole edildi. Olguların %86,4'nda (n=38) tek mikroorganizma, %13.6 (n=6)'nda iki mikroorganizma etken olarak izole edildi. İzole edilen suşların %96'sının (n=48) gram negatif bakteri olduğu saptandı. Çalışmamızda en sık izole edilen gram negatif ajan *Pseudomonas Aeruginosa* (%32) iken bunu *Klebsiella pneumonia* (%24) ve *Acinetobacter baumannii* (%22) izlemekte idi. Genel antibiyotik duyarlılığı incelendiğinde mikroorganizmaların en hassas olduğu antibiyotikler sırasıyla Kolistin (%92,6), Piperasilin-tazobaktam (% 71,4), Amikasin (%65,2) ve Gentamisin (%52,2) olarak saptandı. *Enterobacteriaceae* ve *Acinetobacter* suşlarında Kolistin direnci görülmezken *P. aeruginosa* izolatlarında, kolistin direnci %13 olarak saptandı.

Sonuç: Ventilatör ilişkili pnömonidee, etkili ampirik antibiyotik tedavisi için her ünitenin kendi florasının direnç özelliklerini bilmesi gerekmektedir.

Anahtar Kelimeler: Ventilatör ilişkili pnömoni, çocuk yoğun bakım, mikroorganizma, antibiyotik

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Introduction

Ventilator-associated pneumonia (VAP) is defined as nosocomial pneumonia developing after 48-72 h in patients undergoing mechanical ventilation in the intensive care unit (ICU) [1]. VAP accounts for >90% of all infections in such patients [2].

Bacterial colonization of the upper respiratory tract and gastrointestinal system and aspiration of contaminated secretions into the lower respiratory tract play important roles in VAP pathogenesis. Prior antibiotic use, application of invasive procedures, use of drugs affecting gastric empty-

ing and pH, aspiration of gastric contents, prolonged mechanical ventilation, patient position, severity of underlying illness; central nervous system disorders, frequent changes of endotracheal tubes, and presence of coma, pneumonia, and acute respiratory distress syndrome are among the factors predicting VAP development [3]. VAP is an important cause of morbidity and mortality in patients in the ICU [4].

It is essential to catalog the antibiotic resistance profiles of bacteria present in the ICU to ensure effective planning of an empirical antibiotic therapy for VAP patients.

The aim of the present study was to determine the prevalence of VAP in a pediatric ICU, the pathogens involved, and their antibiotic resistance/susceptibility patterns.

Materials and Methods

This retrospective study evaluated patients diagnosed with VAP in the pediatric ICU (PICU) of Kayseri Training and Research Hospital between January 1, 2014, and June 30, 2016. The study was approved by the local ethics committee. Data were extracted from electronic records, the active surveillance registry, and patient files. The PICU of Kayseri Teaching Hospital has 12 tertiary and 10 secondary beds. The mechanical ventilators used in the PICU feature twin air heaters, an automated valve-based humidification unit with a heater and a dual check system, and a closed aspiration module. The study population included patients between the ages 1 month and 16 years diagnosed with VAP based on the clinical and laboratory findings and who underwent mechanical ventilation for more than 48 h in the PICU. VAP was diagnosed based on clinical, microbiological, and age-related radiological criteria, wherein at least one of the following was 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. These signs were a change in sputum characteristics, an increase in the amount of respiratory secretion or in suctioning requirements, new-onset or worsening cough, dyspnea or tachypnea, rales or 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 need for ventilation] (Table 1). The aforementioned characteristics are the VAP criteria of the Center for Disease Control and Prevention (CDC) [5].

Table 1. Diagnostic criteria for ventilation-associated pneumonia in children

Criteria for those aged <1 year

Decreased oxygen saturation, increased oxygen demand, or increased ventilator requirement and

Presence of at least three of the criteria provided below:

1. Irregularity in fever without a recognized cause
2. Leukopenia (<4000 cells/mm^3) or leukocytosis (>15,000 cells/mm^3) and band ratio ≥% 10
3. New-onset purulent sputum, change in sputum characteristics, increased respiratory secretions, or increased need for aspiration
4. Apnea, tachypnea, or retractions in the chest wall
5. Wheezing, rales, or rhonchi
6. Cough
7. Bradycardia (<100 pulse/min) tachycardia (>170 pulse/min)

PLUS

Presence of a radiological criterion:

1. New or progressive infiltration, consolidation, cavitation, or pneumatocele on at least two serial chest radiographs

Criteria for those aged >1 year

Presence of at least one clinical criterion provided below:

1. Episode of fever without a recognized cause (38°C)
2. Leukopenia (<4000 cells/mm^3) or leukocytosis (>15,000 cells/mm^3) and

Presence of at least two of the criteria provided below:

3. New-onset purulent sputum or change in sputum characteristics, increased respiratory secretions, or increased need for aspiration
4. New-onset or worsening cough or dyspnea, apnea, or tachypnea
5. Rales or bronchial breathing sounds
6. Decreased oxygen saturation, increased oxygen demand, or increased ventilator requirement

We recorded patient age, sex, underlying chronic diseases, use of H_2-receptor antagonists, and head position, as well as adherence to hand hygiene protocols by healthcare professionals. The leukocyte count and C-reactive protein (CRP) and procalcitonin levels at diagnosis were also noted.

VAP prevalence and mechanical ventilation frequency were calculated using the formulas of the National Hospital Infections Surveillance Control Unit: VAP prevalence=number of VAP patients/ventilator days×1,000; rate of mechanical ventilation=ventilator days/patient days; and VAP ratio=number of VAP cases/total number of hospitalized patients. Bronchoalveolar (BAL) samples were obtained using mini-BAL catheters (Combicath, Plastimed Laboratory Saint Leu La Forêt Cedex, France). Bacterial levels of >10^4 colony-forming units upon quantitative culture were considered significant. Microorganisms were identified and their antibiotic susceptibilities were explored using an automated VITEK 2 system (BioMerieux Inc.; Mercy L'etoil, France) by following the protocols dictated by the Clinical and Laboratory Standards Institute [6].

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA). Data normality was evaluated using the Kolmogorov-Smirnov test. Nonparametric data are expressed as median (minimum-maximum).

Results

A total of 44 patients were diagnosed with VAP between January 1, 2014, and June 30, 2016. During this period, 1,151 patients were hospitalized for 10,245 days; the number of ventilator days was 5,786. Of all the patients, 47.7% were females (n=21) and 52.3% were males (n=23). The median age was 42 (3-199) months. The median length of PICU stay was 204 (19-917) days, and the median number of ventilator days was 112 (19-562). The frequency of mechanical ventilation was 56.5%. The VAP prevalence was 8.6 patients per 1,000 ventilator days. The rate of adherence to hand hygiene procedures was 64.4±3.1%. At diagnosis, the mean leukocyte count was 15,240±6,500 cells/mm^3, and the median procalcitonin and CRP levels were 3.16 (0.05-54.33) ng/mL and 56.9 (3.17-369) mg/

Table 2. Isolated microorganisms (n=50)

Causative agent	n (%)
Pseudomonas aeruginosa	16 (32.0)
Klebsiella spp.	12 (24.0)
Acinetobacter baumannii	11 (22.0)
Enterobacter aerogenes	2 (4)
Alcaligenes faecalis	2 (4)
Serratia marcescens	2 (4)
Escherichia coli	2 (4)
Bordetella bronchiseptia	1 (2)
Stenotrophomonas maltophilia	1 (2)
Corynebacteria ssp.	1 (2)
Total	50 (100)

Table 3. Overall antibiotic susceptibilities

Antibiotic	Susceptible (%)	Resistant (%)
Colistin	92.6	7.4
Piperacillin-tazobactam	71.4	28.6
Amikacin	65.2	34.8
Gentamicin	52.2	47.8
Ceftazidime	48.6	51.4
Imipenem	39.1	60.9
Ciprofloxacin	37.0	63.0
Cefepime	32.6	67.4
Meropenem	15.2	84.8
Ceftriaxone	13.0	87.0
Tigecycline	8.9	91.1

Table 4. Isolated microorganisms (n=50)

Causative agent	n (%)
Pseudomonas aeruginosa	16 (32.0)
Klebsiella spp.	12 (24.0)
Acinetobacter baumannii	11 (22.0)
Enterobacter aerogenes	2 (4)
Alcaligenes faecalis	2 (4)
Serratia marcescens	2 (4)
Escherichia coli	2 (4)
Bordetella bronchiseptia	1 (2)
Stenotrophomonas maltophilia	1 (2)
Corynebacteria spp.	1 (2)
Total	50 (100)

mL, respectively. Underlying chronic diseases were detected in 75% of the patients diagnosed with VAP. All such patients had neurological disorders. The elevation of the head position was <30° in 61.4% (n=27) of patients. Of all patients, 75% (n=33) were on H_2-receptor antagonists. All patients underwent mechanical ventilation, 25% (n=11) were transferred to non-ICU wards and 33 (75%) died.

A single microorganism was isolated from 86.4% of patients (n=38), whereas two microorganisms were isolated from 13.6% (n=6). Overall, 96% (n=48) of the isolated strains were gram-negative and 4% (n=2) gram-positive. The most common gram-negative pathogen was *Pseudomonas aeruginosa* (32%), followed by *Klebsiella pneumoniae* (24%) and *Acinetobacter baumannii* (22%; Table 2). Most organisms (92%) were susceptible to colistin (92.6%), followed by piperacillin–tazobactam (71.4%), amikacin (65.2%), and gentamicin (52.2%; Table 3). Of the *Enterobacteriaceae* strains, all (100%) were susceptible to colistin, and some were susceptible to gentamicin (88%), meropenem (88.8%), amikacin (83.3%), ciprofloxacin (77.8%), and ceftazidime (22.2%; Table 3). Of the *Pseudomonas* strains, all (100%) were susceptible to amikacin, and some were susceptible to ciprofloxacin (87.5%), colistin (87.5%), gentamicin (87.3%), ceftazidime (50%), and cefepime (31.3%; Table 3). Of the *Acinetobacter* strains, all (100%) were susceptible to colistin, and some were susceptible to piperacillin-tazobactam (50%); All strains were resistant to amikacin and meropenem (Table 4).

Discussion

Ventilator-associated pneumonia is associated with significant mortality and morbidity. Edwards et al. [7] found that VAP prevalence in PICUs in the USA was 0%-3.2% in both 2006 and 2007. Magill et al. [4] reported that VAP prevalence was 6.89-8.79 patients per 1,000 ventilator days. In Turkey, the National Surveillance report of 2015 estimated VAP prevalence in PICUs as 4.7 patients per 1,000 ventilator days [8]. Furthermore, in Turkey, Şevketoglu et al. [9] reported that VAP prevalence was 4.3 patients per 1,000 ventilator days. In our present study, it was 8.6 patients per 1,000 ventilator days comparable to the data previously reported in the literature. We used the revised 2008 CDC criteria to diagnose VAP [5]. Diagnostic criteria were first established by the CDC in 1988 and were revised in 1992, 2002, 2008, 2013, and 2014. The infection prevalence rates reported in previous studies change to some extent when the January 2014 CDC criteria are applied [10]. VAP prevalence was rather higher in our study for at least two reasons: 1) we used the 2008 CDC diagnostic criteria and 2) we included VAP caused by ventilator-associated events.

Anti-infection strategies are important in PICUs. Hand hygiene and the use of protective gloves and clothing decrease VAP prevalence. The patient's head should be elevated by 45°, and gastric distension should be avoided. Ventilator circuits should not be changed unless essential. Early tracheostomy should be considered for patients who are expected to require a pro-

longed period of mechanical ventilation. Hand hygiene is important to minimize contact transmission [11]. Staff training is equally essential, as is prospective nosocomial surveillance.

The circuit, humidification system, and aspiration method used by mechanical ventilators directly affect VAP development. Filter-mediated passive humidification decreases the incidence of VAP compared with humidification systems employing heaters [12]. In our ICU, humidification is achieved using a dual-check valve-based unit with a heater and an automated water supply system. We suggest that this does not enhance the frequency of VAP; it is unnecessary to open the chamber to replace water, as the system is closed at all times. The twin-heater circuit minimizes water accumulation, and moisture, if any, is drained from the expiration line [13]. The frequency of VAP did not differ when circuits with or without heaters were employed [12, 13]. Previous studies have shown that closed aspiration systems considerably reduce the incidence of VAP compared with open systems [12, 14]. We use closed systems exclusively. Training in hand hygiene effectively reduces VAP prevalence [3]. Poor adherence to hand hygiene protocols may have contributed to VAP development in our PICU. Several factors affect VAP-associated mortality, including the microorganism, comorbid disease, immune response, and the time of VAP onset. Yalçınsoy et al. [15] estimated VAP-related mortality as 42% in an adult ICU. Bor et al. [16] found that VAP-related in-hospital mortality was 71.4%. In our study, mortality was 75%.

The presence of an underlying disease increases the risk of VAP development. Neurological diseases prolong the need for mechanical ventilation and length of ICU stay. In addition, loss of swallowing function increases the level of secretions [17]. Most hospitalized patients have underlying chronic diseases, resulting in prolonged mechanical ventilation and long ICU stays [14]. In our present study, 75% of patients with VAP had an underlying neurological disease, partially explaining the high prevalence of the condition.

H_2-receptor blockers increase the risk of VAP development; such drugs are thus not routinely recommended for ICU patients. Drugs minimizing stress-related ulcer development (by reducing gastric acidity) increase the risk of VAP by enhancing the probability of microbial gastric colonization. Although the data are inconclusive, the routine use of such drugs should be avoided [18]. H_2-receptor blockers were administered to 75% of the VAP patients in our PICU.

Head position is important when seeking to prevent VAP. Elevation of the head by 30° reduces the VAP risk by ensuring that the secretions are drained. All patients under mechanical ventilation should be placed in a sitting position with the head elevated by at least 30°. This position should be maintained even during transport [19]. In our study, 61.4% of patients were not appropriately positioned.

Multibacterial isolates were rare in our study. Such isolates may reflect genuine coinfection or may be attributable to contamination. However, the clinical and laboratory features suggested that contamination was not involved, because the mini-BAL technique was used to isolate the causative agents. The interpenetration of the two catheters minimizes the contamination risk [20]. gram-negative bacteria are the principal cause of VAP (98% of our cases) [21]. The most common gram-negative agent was *P. aeruginosa*, followed by *K. pneumoniae* and *A. baumanii*. Epidemiological studies have revealed a close relationship between the use of antimicrobials and the development of drug resistance. Thus, we assessed microbial antibiotic susceptibilities. Carbapenems are broad-spectrum antibiotics commonly used in ICUs. We found that carbapenem resistance was widespread among gram-negative bacteria. In recent years, carbapenem-resistant bacteria have become increasingly common both internationally and nationally. Xu et al. [21] found that 4.2% of *Pseudomonas* strains were carbapenem resistant. Yilmaz et al. [22] reported that 21% of *Pseudomonas* strains were imipenem resistant. In our study, the level of imipenem resistance was 88% and that of meropenem resistance 63% among the *Pseudomonas* strains. Thus, our frequency of carbapenem resistance was considerably higher than that reported to date. In addition, all *Acinetobacter* strains were resistant to meropenem. The high frequency of carbapenem resistance may be attributable to the empirical or targeted carbapenem use in patients suspected to be infected with gram-negative bacteria, the failure of control or isolation measures, or selection of resistant strains during antibiotic therapy [23]. In recent years, colistin has been increasingly used to control drug-resistant strains of *P. aeruginosa* and *A. baumanii*. Colistin has toxic side effects, and its effectiveness is poor when used to treat pulmonary infections. Yilmaz et al. [22] found that 51.8% of *A. baumanii* and 32.1% of *P. aeruginosa* strains were colistin resistant. In our study, no colistin resistance was detected among enterobacterium or *Acinetobacter* strains; however, 13% of *P. aeruginosa* strains were resistant [24]. Amikacin, an aminoglycoside, is highly effective when used to treat *Pseudomonas* infections, because the drug is susceptible to the actions of only a few aminoglycoside-modifying enzymes. Aminoglycoside resistance has been reported in 0%-51% of *P. aeruginosa* strains [25]. In our study, no amikacin resistance was detected among *Pseudomonas* strains; however, all *Acinetobacter* strains were resistant.

In conclusion, VAP is significantly associated with ICU mortality. Development of antibiotic resistance is influenced by the hospital setting, patient characteristics, the nature and frequency of the invasive procedures performed, and the use of antibiotics. It is essential to catalog the bacterial flora prevalent in the ICU when seeking to plan an effective empirical antibiotic therapy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine (Decision No: 2017/125).

Informed Consent: Written informed consent was not obtained from patients due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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