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Analysis of epidemiology and risk factors for mortality in ventilator-associated pneumonia attacks in intensive care unit patients

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Background/aim: The aim of this study was to investigate the epidemiologic characteristics, the causative microorganisms and their antimicrobial susceptibility patterns, and the prognostic risk factors for mortality in critically ill patients with ventilator-associated pneumonia (VAP).

Materials and methods: In this retrospective observational study, all the critically ill patients with VAP hospitalized in a medical/surgical intensive care unit (ICU) between January 2010 and June 2015 were evaluated. Patients' demographic features and microbiological data were reviewed.

Results: A total of 417 patients were clinically diagnosed with VAP; 51.1% of them were male and the average age was found as 69.9 ± 15.9 years. VAP was detected at approximately 25.0 ± 18.0 days of ICU stay and 17.9 ± 12.6 days after intubation. *Acinetobacter baumannii* (69.5%) was isolated as the most frequent VAP agent, and the most effective antibiotic was colistin. The crude mortality rate was detected as 39.8% among the patients. The presence of dyspnea at admission, coronary heart disease as a comorbidity, unconsciousness at admission, steroid usage, and prolonged hospital stay were observed as independent risk factors in multivariate analysis ($P < 0.01$).

Conclusion: According to the etiological microorganisms and antimicrobial susceptibility patterns, colistin was found to be the most reliable antibiotic for empirical antimicrobial therapy.

Key words: Ventilator-associated pneumonia, intensive care units, risk factors

1. Introduction

Ventilator-associated pneumonia (VAP) is a nosocomial infection that appears in patients who have invasive mechanical ventilation (IMV). It is frequently seen in intensive care units (ICUs) and has a high mortality rate. Some predetermined risk factors such as underlying diseases, age, sex, and the need for intubation in the emergency room as well as modifiable risk factors such as the use of nasogastric tubes, enteral feeding, and IMV for more than 2 days are associated with the development of VAP. It is possible to decrease VAP incidence by improving the modifiable risk factors. Regular surveillance for VAP, as done for other nosocomial infections, is very important to prevent VAP development (1). Hospital and ICU stays are prolonged due to VAP. Pathogenic agents and antibiotic susceptibility patterns vary among different centers, and administration of appropriate antibiotherapy by taking those antibiotic susceptibility patterns into consideration significantly decreases VAP-related mortality rates (2). It was reported that insufficient use of antibiotics resulted in a mortality rate of 69.2%; however, this rate decreased to 46% with the use of appropriate antibiotics (3). Therefore, it has been recommended that every center should determine its own empirical treatment protocol (2). In this retrospective study, we aimed to determine the epidemiologic characteristics, causative microorganisms and their antimicrobial susceptibility patterns, and prognostic risk factors for mortality in VAP attacks in patients hospitalized in the medical/surgical ICU of our hospital.

2. Materials and methods

This retrospective observational study was conducted at the medical/surgical ICU of Ankara Numune Research and Training Hospital for the period of January 2010 to June 2015. This hospital is a referral hospital and there were

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25 adult ICU beds in this unit. The ICU accommodated all the critically ill patients except for the coronary heart disease patients. The authors collected 5.5 years of prospective surveillance data from this ICU. Surveillance data were retrieved from the hospital's infectious control data registry.

A VAP attack was defined as pneumonia that developed 48–72 h after patients had been intubated and received mechanical ventilation in patients who did not have pneumonia at admission. VAP diagnosis was based on clinical and/or microbiological criteria of a new or persistent infiltration on chest X-ray, a body temperature of >38.5 °C or <35 °C, a white blood cell count of >10,000/mm^3 or <5000 mm^3, purulent tracheobronchial secretion, and isolation of a pathogenic agent from the endotracheal aspiration (4). The diagnosis of VAP was established by quantitative culture (≥10^5 colony-forming units/mL in the effluent).

A detailed history including the name, age, sex, underlying clinical condition, date of admission to the ICU, treatment being administered in the ICU, length of stay in the ICU, duration of IMV days, and clinical outcome of each patient was noted. Besides these demographic variables, causative microorganisms and antimicrobial susceptibility patterns were also recorded. In the case of more than one VAP attack during an ICU stay, the first attack of the patient was taken into consideration.

3. Results

A total of 417 patients consisting of 213 (51.1%) males and 204 (48.9%) females were included in the study. The mean age of the patients was 69.9 ± 15.9 (range: 19–98) years, the mean hospital stay was 45.59 ± 27.2 (range: 8–154) days, and the mean ICU stay was 40.53 ± 24.1 (range: 8–149) days. The mean duration of ventilator support was 27.10 ± 16.0 (range: 1–142) days. The causes of admission to the ICU were respiratory distress in 390 (93.5%) patients with poor general condition in 40.5%, cerebrovascular disease (CVD) in 12.5%, trauma in 7.4%, and some other health problems in 7.2% of the patients. There was comorbid disease(s) in 384 (92.1%) patients. The most frequent comorbid diseases were hypertension (HT) (57.8%), CVD (39.3%), diabetes mellitus (DM) (35.3%), chronic obstructive pulmonary disease (COPD) (27.3%), coronary heart disease (CHD) (22.8%), and chronic renal failure (CRF) (16.8%). There was a solid tumor in 62 (14.9%), a hematological malignity in 9 (2.2%), and steroid use in 46 (11.1%) patients. The characteristics of the patients are presented in Table 1.

The distribution of VAP attacks among the years revealed that the attacks occurred most frequently (24.0%) in 2010. The rates of VAP in the following years were 20.6%, 18.7%, 13.4%, 15.1%, and 8.2% respectively.

Table 1. The clinical characteristics of the patients with VAP.

Characteristic	Number	%
Age (years), mean	69.9	(19–98)
Sex		
Female	204	48.9
Male	213	51.1
Cause for hospitalization		
Respiratory distress	390	93.5
Poor general condition	169	40.5
Cerebrovascular disease	52	12.5
Trauma	31	7.4
Othe	30	7.2
Intoxication	1	0.2
Comorbid disease		
Hypertension	241	57.8
Diabetes	147	35.3
COPD	114	27.3
CRF	70	16.8
CAD	95	22.8
Solid tumor	62	14.9
Hematological malignity	9	2.2
CLD	8	1.9
Steroid use	46	11.1
Previous surgery	55	13.2

COPD: Chronic obstructive pulmonary disease, CRF: chronic renal failure, CAD: coronary artery disease, CLD: chronic liver disease.

The most frequently isolated agent during the study period was *Acinetobacter baumannii*, which was isolated in 290 (69.3%) patients. The carbapenem resistance rate was found as 99.4% in *A. baumannii* strains, and the agents were the most susceptible to colistin. The rates of resistance of *A. baumannii* strains to other antimicrobials were as follows: meropenem 99.7%, piperacillin/tazobactam 99.3%, amikacin 93.1%, ciprofloxacin 99.7%, and ceftazidime 99.3%. Other agents that were isolated as the causative agents of VAP were *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The antimicrobial resistance rates of *P. aeruginosa* strains were as follows: meropenem 54.1%, piperacillin/tazobactam 52.7%, amikacin 29.7%, ciprofloxacin 50%, ceftazidime 45.9%, and colistin 1.4% (Table 2).

The crude mortality rate was found as 39.8%. Univariate analysis performed to determine the risk factors for mortality determined that CAD, presence of

Table 2. The antibiotic resistance rates of the isolated agents.

	A. baumannii	*Pseudomonas* spp.
Antibiotic		
Carbapenem	99.7%	54.1%
Piperacillin/tazobactam	99.3%	2.7%5
Amikacin	93.1%	29.7%
Ciprofloxacin	99.7%	50%
Ceftazidime	99.3%	45.9%
Colistin	0.7%	1.4%

a solid tumor, and use of corticosteroids were significant predictors of mortality. Respiratory distress and poor general condition as the causes for admission to the ICU, unconsciousness during admission to the ICU, prolonged ICU stay, and isolation of *A. baumannii* as the causative agent for VAP were also significant predictors for mortality ($P < 0.005$). The presence of dyspnea at admission (HR: 0.39, 95% CI: 0.17–0.92; $P = 0.031$), coronary heart disease as a comorbidity (HR: 2.03, 95% CI: 1.25–3.28; $P = 0.004$), unconsciousness at admission (HR: 0.57, 95% CI: 0.36–0.89; $P = 0.013$), steroid usage (HR: 2.66, 95% CI: 1.39–5.12; $P = 0.003$), and prolonged hospital stay (HR: 1.01, 95% CI: 1.01–1.02; $P = 0.003$) were observed as independent risk factors in multivariate analysis (Table 3).

4. Discussion

VAP is a frequently seen severe nosocomial infection. It should be diagnosed and treated immediately after its development (5,6). There may be differences in the incidence of VAP even in the same clinic in different time periods. Therefore, regular examination of the incidence is important for both taking the necessary precautions and to observe the alterations in the outcomes. VAP-related

Table 3. Univariate and multivariate analysis of the risk factors for mortality in patients with VAP.

	Dead	Alive	Univariate analysis	Multivariate analysis	
			P	P	OR (95% CI)
Age (years)	71.2 ± 15.5	68.6 ± 16.2	0.1		
Being male	25	126	0.644		
Complaint on admission					
· Poor general condition	78	90	0.032		
· Dyspnea	149	240	0.014	0.031	0.39 (0.169–0.917)
· CVA	18	34	0.451		
· General body trauma	7	24	0.055		
· Intoxication	0	1	1.00		
Comorbid disease					
· COPD	48	66	0.577		
· CHD	49	46	0.009	0.004	2.03 (1.252–3.278)
· DM	53	93	0.295		
· Solid tumor	32	29	0.034		
Predisposing factors					
· Central venous catheter	59	81	0.526		
· Steroid use	28	18	0.004	0.003	2.66 (1.387–5.115)
· History of surgery	22	33	1.00		
Physical examination					
· Unconsciousness	106	183	0.050	0.013	0.57 (0.360–0.887)
Hospital stay (days)	48.9 ± 28.4	40.8 ± 24.5	0.003	0.003	1.01 (1.005–1.024)
IMV duration (days)	27.1 ± 17.3	27.1 ± 15.1	0.012		
Isolation of *A. baumannii* as the causative agent	124	162	0.040		

mortality has been reported as 13%–70% (7). Other studies reported this rate as 52.6%–59.4% (7–9). In our study, the mortality rate related to VAP was found as 39.8%, in accordance with the literature.

A number of studies indicated that sex did not have any effect on the development of VAP (10,11). However, some others claimed that VAP occurred in males more frequently (12,13). In our study, we did not find any effect of sex on the development of VAP. Similarly, there is no consensus on the effect of the age of the patients. Some studies reported that age was not a significant factor for VAP development while some others claimed that an old age alone increased the risk of VAP (8,12,14,15). In our study, we determined that the patients that were diagnosed with VAP were elderly patients; however, age was not found as a risk factor for mortality.

Agarwal et al. investigated the effect of diagnosis at the time of admission on the development of nosocomial infections. They reported that admission to the ICU with the diagnosis of a community-acquired infection increased the development of nosocomial infections (10). Some studies determined respiratory distress as a risk factor for VAP (11,16). However, some others did not determine any correlation between the diagnosis at admission and development of VAP (15). An important finding of our study is the determination of respiratory distress and poor general condition as the primary diagnosis upon admission as the risk factors for mortality. In addition, respiratory distress and unconsciousness at admission were found as independent risk factors for mortality. Since the general conditions of the patients with severe respiratory distress and unconsciousness are poor, they might need more intensive and heavy treatment. In addition to these factors, a need for more invasive procedures may necessitate earlier intubation in those patients. All those factors were suggested to increase mortality in patients with VAP.

Comorbid chronic diseases may be risk factors for the development of VAP. The most important of those are HT, CHD, and DM (8,14,17,18). COPD and CRF may also be risk factors for VAP development. Ibrahim et al. found CHD as a risk factor for both VAP and mortality (13). Agarwal et al. determined CRF as a risk factor for the development of VAP (10). On the other hand, Carrilho et al. of Brazil did not find any significant correlation of CHD or CRF with development of VAP (19). In our study, we investigated the correlation of comorbid diseases with mortality in patients with VAP. CHD was found as an independent predictor of mortality in those patients. It was supposed that CHD as a comorbid disease could facilitate the development of heart failure and hence increase mortality in patients with VAP.

Immunosuppression may be an important risk factor for both community-acquired and nosocomial infections. It was hypothesized that corticosteroids and other immunosuppressive agents could establish a ground for infection by impairing host defense mechanisms, and some studies supported this hypothesis (10,17,20). Similarly, in our study, corticosteroid use was found as an independent predictor of mortality. However, a multicenter point-prevalence study performed in Turkey did not find the use of corticosteroids as a risk factor for acquiring infections in the ICU (21). We also investigated the presence of malignant disease as a risk factor for mortality. Univariate analysis results indicated that the mortality rate was significantly higher in patients with solid tumors after VAP attacks. A similar result was not obtained for the presence of a hematological malignity, and this result was thought to be due to the small number of patients with hematological malignant diseases.

Prolongation of ICU stay and intubation causes higher VAP incidence and mortality rates (10,22–25). As the length of stay at the hospital is prolonged, the patients have more chances to get hospital-acquired infections. Prolonged length of stay was found as an independent risk factor at the end of our study, which was consistent with the literature.

The distribution of the microorganisms causing VAP shows variations in accordance with the definitions of early and late pneumonia. The roles of particularly *P. aeruginosa*, *S. aureus*, and *Enterobacteriaceae* spp. have been emphasized in the literature (26). A multicenter study conducted in Turkey determined *Acinetobacter* spp. as the most frequent cause of VAP, followed by *P. aeruginosa*, and *S. aureus* (27). The most frequently isolated organism in our study was *A. baumannii* (72.4%), followed by *Pseudomonas* spp. (16.9%). The resistance rate to carbapenem was found as 99.4% in *A. baumannii* strains, and colistin was found to have the highest susceptibility rate.

In conclusion, VAP is a preventable infectious disease with high morbidity and mortality, and it increases hospital stay and treatment costs and brings a burden to the country's economy. Mortality is a significant problem in these patients. In patients with a number of comorbid diseases who are intubated in the ICU, VAP may develop and may be fatal. One of the most important factors to decrease mortality is to prevent VAP. Use of effective infection control measures, regular analysis of surveillance results in every unit, the taking of necessary precautions, and the administration of appropriate and correct empirical treatment may decrease the mortality rate.

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