Evaluation of risk factors in patients with ventilator-associated pneumonia caused by Acinetobacter baumannii

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ABSTRACT

Purpose: Ventilator-associated pneumonia is a significant disease with high mortality rates. Acinetobacter baumannii is one of the most critical pathogens leading to ventilator-associated pneumonia. This study aims to evaluate the underlying risk factors in patients diagnosed with ventilator-associated pneumonia caused by Acinetobacter baumannii, who were followed in intensive care units of our hospital.

Patients and Methods: The data of 112 patients diagnosed with ventilator-associated pneumonia caused by Acinetobacter baumannii, who were followed in Intensive Care Units other than Pediatric Intensive Care Unit of our hospital from 2013 to 2017, were evaluated retrospectively.

Keywords: Ventilator-associated pneumonia, Acinetobacter baumannii, Pneumonia.

Cite this Article: Baran, A.I., Çelik, M., Arslan, Y., Demirkiran, H., Sünetçioğlu, M., Sünetçioğlu, A. 2020. Evaluation of risk factors in patients with ventilator-associated pneumonia caused by Acinetobacter baumannii. Bali Medical Journal 9(1): 125-130. DOI: 10.15562/bmj.v9i1.1751

INTRODUCTION:

Lower respiratory tract infections that are not present at the time of hospital admission but develop 48-72 hours after intubation in patients staying at the intensive care unit (ICU) are called ventilator-associated pneumonia (VAP). ¹ VAP is a severe infection which is very common in ICU and has a high mortality. The pathogenesis of VAP in ICU includes the impairment of the effectiveness of the upper respiratory tract and other defence mechanisms. The pathogenesis of VAP could be associated with an endotracheal tube, decreased cough reflex, oropharyngeal colonization, deterioration of ciliary functions, uremia, hypoxia, malnutrition, ventilation-perfusion mismatch, and insufficient endotracheal aspiration.² Microorganisms leading to VAP are Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenza in the early-onset VAP (occurring within 96 hours following the mechanical ventilation application) and methicillin-resistant Staphylococcus aureus (MRSA), Klebsiella spp., Pseudomonas aeruginosa and Acinetobacter baumannii in the late-onset VAP (occurring after 96 hours following the mechanical ventilation application).³ Acinetobacter baumannii is a species frequently leading to severe infections, which is characterized by the highest antibiotic resistance.⁴ The most important risk factors for Acinetobacter infections are mechanical ventilation, ICU stays and broad-spectrum antibiotic use.⁵ Acinetobacter spp. causes severe diseases such as VAP, urinary tract infection, wound site infection, bloodstream infection, endocarditis and meningitis.⁶ This study aims to evaluate the underlying risk factors in patients diagnosed with VAP caused by Acinetobacter baumannii, who were followed in ICUs of our hospital, except for pediatric ICUs.

MATERIAL AND METHODS:

This was a cohort retrospective study by total sampling technic. The data of 112 cases, who were followed in ICUs other than pediatric ICU’s of our hospital between 2013-2017, aged 18 years and above, diagnosed with VAP, and had resistant Acinetobacter baumannii growth in sincere
tracheal aspiration (DTA) culture, were analysed retrospectively. All cases with *Acinetobacter baumannii* growth were evaluated according to age, gender, diagnosis at admission to the intensive care unit, the day when the bacterial growth occurred following the invasive mechanical ventilation, the presence of modifiable and non-modifiable risk factors (at the time of admission), mortality, laboratory results (results obtained at the time of VAP diagnosis). The VAP diagnosis was made based on the presence of the following criteria: ≥10^5 CFU/mL growth in the quantitative culture of endotracheal aspirate, new or developing purulent sputum, and the development of new or progressive infiltration in the chest X-ray.

Modifiable risk factors were considered as the use of nasogastric probe (NG), the use of proton pump inhibitor (PPI) and anti-acid, presence of invasive mechanical ventilation lasting more than 48 hours, presence of tracheostomy, use of more than two units of blood product, and presence of immunosuppressive agents. Non-modifiable risk factors (at the time of admission) were determined as follows: age, gender, and the presence of any of the following conditions: chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), history of the cardiovascular system, trauma, and malignancy. The term VAP-associated mortality was used to identify patients who died due to any reason following the VAP diagnosis. Ethics Committee of Van Yuzuncu Yil University has approved this study.

**RESULTS:**

Of the patients included in our study, 79 (70.5%) were male, and 33 (29.5%) were female. The mean age was 53.8 ± 15.93 (23-80), whereas the mean age of male and female patients was 53.3 ± 15.93 (23-78) and 55 ± 16.10 (25-80), respectively. Of the cases, 98 (87.5%) were followed in Anaesthesiology and Reanimation ICU, 12 (10.7%) were observed in Neurology ICU, one patient (0.9%) was observed in Cardiovascular Surgery ICU, and one patient (0.9%) was followed in Cardiology Coronary ICU (Table 1).

The most common reason for admission to ICU was trauma (intravehicular or extravehicular traffic accident, gunshot injuries, falling down from height) with 33 cases (29.5%). The second most frequent reason was COPD exacerbation and respiratory distress with a rate of 13.4%, which was followed by post-operative follow-up of gastrointestinal/genitourinary system with a percentage of 13.3%. The time between the day of mechanical ventilation and day when the growth in DTA culture was detected was 20.8 days.

In our antibiotic resistance profile, there was only one case (extensively-drug resistant [XDR]) resistant to antibiotics, including colistin. The most commonly used combination in antibiotic therapy was colistin + meropenem combination with 42 cases (37.5%). Acute renal failure (ARF) was developed in 19 cases (17%) following the colistin use.

When the modifiable risk factors were evaluated, mechanical ventilation and antacid were found to be used in all cases. Furthermore, presence of urinary catheters was in 109 cases (98.2%), NG probe was applied in 102 cases (91%), more than two units of blood product support was used in 51 cases (45.5%), tracheostomy was found to be used in 43 patients (38.4%). The use of immunosuppressive agent was in 23 cases (20.5%). When non-modifiable risk factors were evaluated, 34 (30.4%) cases had trauma, 33 (29.5%) cases had cardiovascular disease history, 22 cases (19.6%) had malignancy, 20 cases (17.9%) had COPD, and 20 cases (17.9%) had DM. Of the cases, 46 (41.1%) were in the older age group (older age accepted as >60 years old) (Table 2).

The mean values of the laboratory test results of the cases were found as follows: white blood cell count: 14900 ± 5460 µL (4000-9.000), hemoglobin: 9.9 g/dL (female: 1), platelet: 230.000 µL (150.000-450.000), C-reactive protein: 143.8 ±66.3 mg/L (0-5), Alt/Ast: 90/69 U/L (0-41/0-37), T/D bilirubin: 1.2/0.7 mg/dL (0.3-1.2/ 0.1-0.5), creatinine: 1.16 mg/dL (0.9-1.2), and serum albumin level: 2.2 mg/dL (3.5-5). The mean of procalcitonin of 77 cases examined for procalcitonin was 6.18 (<0.5 is normal value). Mean neutrophil/lymphocyte ratio was 13200/1075 µL (Table 3).

In the present study, VAP-related mortality rate was 44% (49 patients) and total mortality rate during the stay at the ICU (due to subsequent infection/comorbid conditions) was 79% (88 patients). Of the patients, 24 patients (21%) recovered after the treatment.

**DISCUSSION:**

Patients followed in ICU are susceptible to infections due to many factors, including age, immunity status, the type and severity of the underlying disease, medications (antibiotics, steroids, chemotherapy, antacids, etc.), impaired consciousness, shock, organ failure, disorders in defensive mechanisms, and invasive procedures. Data from the world and Turkey show that ventilator usage rates are between 0.31-0.71. In a study conducted in Turkey, the mean use of mechanical ventilation was found to be 0.63 and VAP ratio was 26.5, according to 1000 invasive instruments. Ventilator-associated pneumonia is a critical problem that causes prolonged stay in ICUs.
Table 1. Distribution of Patients According to Intensive Care Units

| Type of Unit                        | No of cases | Per |
|------------------------------------|-------------|-----|
| Anesthesiology and Reanimation ICU | 98          | 87.5% |
| Neurology ICU                      | 12          | 10.7% |
| Cardiovascular Surgery ICU         | 1           | 0.9% |
| Cardiology Coronary ICU            | 1           | 0.9% |

Table 2. Modifiable and Non-Modifiable Risk Factors of Patients

| Modifiable Risk Factors | No of cases | Per  | Non-Modifiable Risk Factors | No of cases | Per  |
|-------------------------|-------------|------|-----------------------------|-------------|------|
| Mechanical ventilation  | 112         | 100% | Trauma                      | 34          | 30.4%|
| Antacid use             | 112         | 100% | Cardiovascular disease history | 33          | 29.5%|
| Ng probe apply          | 102         | 91%  | Malignancy                  | 22          | 19.6%|
| Blood product support   | 51          | 45.5%| Older age                   | 46          | 41.1%|
| Urinary catheter apply  | 109         | 98%  | COPD                        | 20          | 17.9%|
| Tracheostomy            | 43          | 38.4%| DM                          | 20          | 17.9%|
| Immunosuppressive agent use | 23      | 20.5%|

Ng probe: Nasogastric probe, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus

Table 3. The Mean Values of The Laboratory Test Results of the Cases

| Test type       | Mean value | Test type       | Mean value |
|-----------------|------------|-----------------|------------|
| White blood cell| 14900 µL   | Creatinine      | 1.1 mg/dL  |
| Hemoglobin      | 9.9 g/dL   | Albumin         | 2.2 mg/dL  |
| Platelet        | 230.000 µL | Procalcitonin   | 6.18       |
| C-reactive protein | 143.8 mg/L | Neutrophil/lymphocyte ratio | 13200/1075 µL |
| Alt             | 90 U/L     | Total bilirubin | 1.2 mg/dL  |
| Ast             | 60 U/L     | Direct bilirubin| 0.7 mg/dL  |

and hospital, cost increase, increase in morbidity and mortality rates. Acinetobacter baumannii is a species frequently leading to severe infections, which is characterized by the highest antibiotic resistance. The followings are among the known risk factors: prolonged hospital stay, mechanical ventilation, underlying diseases, invasive procedures, inadequate inappropriate antibiotic treatment and surgical treatment. Acinetobacter baumannii has been reported to survive for a more extended period on the dry surface compared to Pseudomonas aeruginosa and Staphylococcus aureus. Acinetobacter baumannii is found in the bacterial flora of the skin, particularly in the axillary and inguinal regions, and in the respiratory tract, oral cavity and gastrointestinal tract of healthy individuals. The bacterial carriage has been reported to be higher in hospitalized patients. Permanent carrier status and environmental contamination in hospital staff lead to outbreaks. Acinetobacter baumannii is the principal problematic agent of nosocomial infections in our hospital too, especially in VAP. In a study performed by Kılıç et al. in our hospital, Acinetobacter was found to be the most commonly isolated pathogen in patients diagnosed with VAP. The present study included cases who were diagnosed with VAP caused by Acinetobacter baumannii and were followed in the ICUs of our hospital.

Anesthesiology and Reanimation ICUs are the hospital units where intensive drug therapy is applied due to multiple organ dysfunction, patients undergoing mechanical ventilation are followed, many invasive procedures are needed to be performed, and nosocomial infection and mortality rate is high. Moreover, VAP development risk is higher than the other units because of the more top ventilator use rate in Anaesthesiology and Reanimation ICUs. In the present study, 98 (87.5%) of the cases who developed VAP were followed in the Anaesthesiology and Reanimation ICU.

Although some studies have reported that the majority of patients with VAP are elderly patients, the age factor has been reported to be not an independent risk factor that increases VAP development. In a study by Bonten et al., the development risk of VAP was reported to increase by 5.1 fold in cases older than 60 years. Bilici et al., further showed in their study that advanced age causes an increase of approximately two times more VAP development risk. The mean age in the present study was 53.8 ± 15.93 and 46 (41.1%) patients were in the older age group.

Although there is no significant difference between male and female gender in terms of the prevalence of VAP, Bonten et al., reported in their study that male gender increased VAP development by 2-fold independent of other risk factors. The study included 79 (70.5%) male and 33 (29.5%) female patients. In this respect, male sex dominance may be considered as an independent risk factor for the development of VAP.

Some of the risk factors that play a role in VAP development are modifiable risk factors that are present at the time of admission to the ICU and non-modifiable risk factors that are developed during the stay at the ICU. The longer duration
of mechanical ventilation is one of the critical risk factors for the VAP development. In particular, every day spent on mechanical ventilation increases the risk of VAP by 1–3%. In our study, mechanical ventilation was performed in all of our cases. The mean reproduction time was 20.8 days in DTA culture after mechanical ventilation. Blood transfusion applications have been reported to be risk factors that may lead to the VAP development. In our study, it was seen that approximately half (45.5%) of our patients were provided with blood product support. Enteral feeding via nasogastric tube is thought to be one of the applications increasing the VAP risk. Enteral feeding via nasogastric tube was reported to be the most frequently preferred feeding method in patients with VAP and one of the risk factors that increase the VAP-related mortality. In our study, it was observed that a nasogastric catheter was applied to patients as high as 91% and it was the most common form of enteral feeding. It has been discussed for many years that H2 receptor blockers and proton pump inhibitors can increase gastric pH levels and cause gastric colonization and therefore, they may increase the risk of hospital-acquired pneumonia and VAP. However, some recent studies have shown that this risk does not increase significantly. Taşbakan et al. did not find a relationship between the VAP prevalence and upper gastrointestinal bleeding with the prophylaxis of stress-related mucosal damage (SRMD). In our study, the use of PPI / H2 receptor blockers was 100%. Although the effect of stress prophylaxis methods on the development of VAP is not known in studies, we believe that PPI / H2 receptor blocker usage is very high in our hospital and it is a correct approach to reduce its use. Tracheostomy rates are high in patients with VAP. Early tracheostomy has been shown to be beneficial in patients undergoing prolonged mechanical ventilation. The incidence of VAP was reported to be 5% and 25% in patients who underwent early tracheostomy and patients who underwent tracheostomy 15 days after the mechanical ventilation, respectively. In our study, tracheostomy was observed in 38.3% of cases on the day of VAP diagnosis. In a study performed by Kılıç et al., in our hospital, tracheostomy was performed on the 22nd day of intubation. Still, no significant difference was found between late tracheostomy and VAP development. Blood transfusion applications have been reported to be risk factors in terms of VAP development. Hatipoğlu stated that more than four units of blood product transfusion were a risk factor for the development of VAP. The effects of steroid use on the immune system are known and there are studies indicating that the incidence and severity of VAP have increased in patients using steroid. Öcal et al., reported that steroid users were more tend to develop VAP significantly. In our study, the use of immunosuppressive agents was found to be 20.5% and blood product support was 45.5%. Also, urinary catheter application was present in 98% of the cases.

Some chronic diseases from the risk factors accompanying patients may be a risk factor for VAP. The presence of COPD and DM are the most important ones. Chronic renal failure and heart failure are other risk factors for the development of VAP. In a study by İbrahim et al., heart failure has been shown to be a risk factor for both VAP and mortality. Bilici et al. reported that the prevalence of VAP in patients with COPD was not statistically significant compared to those without COPD. Among the non-modifiable risk factors, 33 cases (29.5%) had a history of cardiovascular system disease, 34 cases (30.4%) had trauma, 22 cases (19.6%) had malignancy, 20 cases (17.9%) had COPD and 20 cases (17.9%) had DM.

In a study by Uslu et al., evaluating the risk factors causing VAP development in their ICUs. The reasons why patients were admitted to ICU were reported to be as follows: respiratory failure in 71.1%, post-surgical care in 11.3%, a trauma in 9.2%, cardiac arrest in 7.8%, and central nervous system infection in 0.7% of the patients. In our study, the most frequent reason for admission to ICU was trauma (29.5%) (intravehicular or extravehicular traffic accident, gunshot injuries, falling down from height). The second most frequent reason was COPD exacerbation and respiratory distress (13.4%) and followed by post-operative follow-up of gastrointestinal/genitourinary system (13.3%).

Among the nosocomial infections, VAP is a critical infectious condition that directly affects mortality. In the literature, there are studies attributing approximately one-third of the deaths to pneumonia in patients with nosocomial pneumonia and reporting mortality rates between 10-65%. In the present study, the VAP-related mortality rate was 44% and it was found to be compatible with the literature.

Acinetobacter spp. can rapidly develop resistance to different antibiotic groups such as beta-lactam antibiotics, tetracycline, fluoroquinolone and aminoglycoside. Since 1980, there has been an increase in multi-drug resistant (MDR) Acinetobacter spp. infections. Sometimes pan-resistant strains lead to severe problems. Resistance to at least two groups of antibiotics in gram-negative bacteria is defined as multiple drug resistance (e.g. cephalosporin and penicillin). In gram-negative bacilli, resistance to all other antibiotics except colistin, tigecycline and aminoglycosides is defined.
as XDR.\textsuperscript{79} In the present study, antibiotic resistance profile evaluation has revealed that there was only one case who was resistant to antibiotics, including colistin.

Treatments combinations have come into prominence, particularly in infections caused by MDR. With the combination of colistin with other antibiotics (imipenem, meropenem, ampicillin-sulbactam, cefepime, piperacillin-tazobactam, aztreonam, aminoglycosides, and quinolones), 76\% success was reported to be achieved in MDR Acinetobacter infections, particularly in patients with VAP.\textsuperscript{80} In the present study, the most commonly used combination therapy was found to be colistin + meropenem combination in 42 cases (37.5\%).

**CONCLUSION**

VAP is a critical condition that prolongs the length of hospital stay and increases the cost of treatment significantly and which is characterized by high mortality and morbidity rates in ICUs. Particularly in cases with VAP caused by Acinetobacter spp., the clinical presentation shows a worse prognosis if the bacterium has MDR and the treatment options in such cases are unfortunately limited. Many measures can be taken to reduce the rates of VAP. The incidence of VAP and VAP-related mortality rates can be reduced by implementing some necessary policies in the VAP prevention guidelines and by knowing and following risk factors closely.

**AUTHOR CONTRIBUTION**

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest regarding the publication of this article.

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