Antibiotherapy and Mortality Rate in Ventilator-Associated Pneumonia and Tracheobronchitis due to Acinetobacter Baumannii

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Objective: Ventilator-associated pneumonia (VAP) due to Acinetobacter baumannii (A. baumannii) has a high mortality rate in the intensive care unit (ICU). The guidelines recommend empirical antimicrobial therapy in cases of VAP; however, similar treatment is not recommended in cases of ventilator-associated tracheobronchitis (VAT) with a culture result of A. baumannii. The aim of this study was to evaluate the difference in the ICU and long-term mortality of patients with A. baumannii VAT and VAP who were treated with antibiotherapy.

Methods: This was a retrospective cohort study. Patients who were intubated in the respiratory ICU due to acute respiratory failure (ARF) and developed A. baumannii-associated VAP or VAT between January 2015 and January 2016 were included in this study. Demographic features, comorbidities, cause of ARF, arterial blood gas values, oxygenation level, chest X-ray findings, ICU severity scores (Sequential Organ Failure Assessment [SOFA] score, Charlson Comorbidity Index score, Acute Physiology and Chronic Health Evaluation II score), culture antibiotic susceptibility results, antibiotic regimen, length of ICU stay, and mortality details were recorded. Long-term mortality (1-, 2-, 3-, 12-month) details were obtained from national death records. The Kaplan-Meier method was used for long-term survival analysis.

Results: Among 503 consecutive patients intubated between January 2015 and January 2016, 78 (15.5%) who had A. baumannii-associated VAT and VAP were included. Of the 78 patients, 21 (35%) were cases of VAP and 50 (65%) were cases of VAT. Diagnoses of the 78 patients were 62% chronic obstructive pulmonary disease, 15% pneumonia, 10% acute cardiogenic pulmonary edema, 9% lung cancer, and 4% kyphoscoliosis. Among the VAP patients, 21 (75%) were male and 7 (25%) were female, while among the VAT patients, 38 (76%) were male and 12 (24%) were female. There was no statically significant difference between the VAP and VAT patients according to age, gender, comorbidities, the presence of acute respiratory distress syndrome or septic shock, Charlson and SOFA scores, or length of hospital and ICU stay. The median (quartile ratio) duration of mechanical ventilator use was 15 days (7–22 days) for VAP patients and 12 days (6–14 days) for VAT patients (p=0.649). The ICU mortality rate was 68% among VAP patients and 40% among VAT patients (p=0.018). The length of the median follow-up after discharge (25%-75%) for VAT patients (n=30) and VAP (n=9) patients was 407 days (34–574 days) and 112 days (34–524 days), respectively (p=0.852). Kaplan-Meier survival analysis was similar for both VAP and VAT patients (p=0.57). The 1-, 2-, 3-, and 12-month mortality in VAT and VAP patients was 11.1% and 16.6% (p=0.69), 44.4%, and 26.7% (p=0.31), 44.4% and 33.3% (p=0.54), and 66.7% and 46.7%, respectively (p=0.29).

Conclusion: Despite antimicrobial treatment for A. baumannii, 2 of every 3 VAP patients and 2 of every 5 VAT patients died. Nonetheless, though antibiotic treatment is not currently recommended for VAT, these results suggest that mortality might be higher in A. baumannii-associated VAT without antimicrobial therapy. Clinical findings and infection markers of patients with VAT due to A. baumannii should be evaluated together and a decision made for patient-specific treatment.
INTRODUCTION

In patients admitted to the intensive care unit (ICU) with respiratory failure, respiratory support is primarily applied as noninvasive mechanical ventilation (NIMV). In general, invasive mechanical ventilation is used in case of failure or contraindication.[1,2] Although it can be life-saving, it is important to be aware of the risks of intubation-related ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT).[3] Studies have revealed an incidence of VAP in the ICU of 10% to 25% with a mortality risk between 25% and 50%, and an incidence of VAT of 1.4% to 11% with a mortality risk of 39%.[4,5]

Another important problem in intubated patients is the increased incidence of multidrug-resistant pathogens due to the use of antibiotic therapy.[6] In recent studies, Acinetobacter baumannii (A. baumannii), has been reported to be the most often seen multidrug-resistant organism to cause the development of VAP and the incidence has increased.[7–9] In addition to contributing to morbidity and mortality rates, A. baumannii outbreaks can lead to the closure of wards and ICUs.[10]

When there is a suspicion of VAP, the American Thoracic Society (ATS) and American Infectious Diseases Association (IDSA) Guidelines of 2005 recommend early and appropriate antibiotic therapy.[11] Recent studies suggest that treatment reduced the conversion to VAP, costs, the length of ICU stay, and time spent on the ventilator.[12–14] However, the initiation of antibiotic therapy is not among the standard treatment options in international guidelines in cases of VAT.[15,16] The 2016 guidelines published by ATS and IDSA do not recommend antibiotic therapy for VAT patients because even though it may reduce the length of an ICU stay and time on a ventilator, it does not alter mortality.[17] Although the guidelines do not suggest antibiotic initiation in VAT, antibiotics have been shown to reduce the development of VAP and associated mortality.[18]

Antibiotic therapy is a well-known risk factor for infection and colonization due to multidrug-resistant organisms.[19] In clinical practice, doctors often attempt to avoid the emergence of multidrug-resistant pathogens with the unnecessary use of broad-spectrum antibiotics, particularly in ICUs. Therefore, the ideal follow-up and management of VAT cases is still unclear. Information about how to regulate antibiotic treatment, especially in the long-term follow-up of VAT cases, is becoming more important. A careful balance is needed between the judicious use of antibiotics to prevent the development of resistant pathogens and avoiding the development of VAP due to the lack of treatment of VAT. VAT is an intermediate condition between lower respiratory tract colonization and pneumonia, and its effect on ICU clinical outcomes is not clear.[13] The mechanisms of formation of VAT and VAP are similar: loss of cough reflex and anatomical barriers due to an endotracheal tube, micro-aspirations of colonized oropharynx and stomach contents, and the contamination of ICU devices. However, it is still unclear whether the clinical and clinical outcomes of VAT cases are distinct from other lower respiratory tract infections (especially VAP) or whether VAT is a risk factor for the development of VAP. In addition to all these uncertainties, a recent histological study demonstrated a relationship between VAP and VAT.[20] Furthermore, in a recent meta-analysis, there was no reduction in mortality in VAT patients who received systemic antibiotic therapy (with or without additional inhaler antibiotics).[21]

This study was designed to test the hypothesis that administering treatment for VAT with A. baumannii as is currently provided for cases of VAP would lead to more positive results in terms of the length of ICU stay day, mortality, and long-term follow-up.

MATERIALS AND METHODS

This study examined the data of a retrospective cohort. The samples of patients in the respiratory intensive care unit (RICU) from between January 2015 and January 2016 with VAT and VAP due to A. baumannii due to acute respiratory failure (ARF) in the respiratory tract were included (Fig. 1). Approval was obtained from the University of Health Sciences Süreyyapaşa Chest Disease and Thoracic Surgery Local Ethics Committee (Date/No.: 08.08.2017/116.2017.007).

Patient identity data were anonymized.

Patients

The records of patients admitted to the ICU due to ARF during the study period were evaluated. Patients with A. baumannii growth in respiratory isolates who were intubated or tracheostomized for more than 48 hours were included in the study (Fig. 1). Cases with signs suggesting infection and diagnosed with pneumonic infiltration on chest X-ray were categorized as VAP, and those that could not be diagnosed were classified as the VAT group. Patients who died during the first 24 hours or who remained less than 24 hours in the ICU, had only NIMV, had no growth in respiratory tract samples, had a growth of A. baumannii growth in respiratory isolates who were intubated or tracheostomized for more than 48 hours, or were younger than 18 years of age were excluded from the study (Fig. 1). Systemic antibiotic therapy (intravenous and/or inhaler) was initiated in both the VAT and VAP cases.

Definitions

VAP: if a new infiltration developed or an increase in the infiltration was detected in patients who have undergone mechanical ventilation for more than 48 hours due to endotracheal intubation/tracheostomy, cases with at least 2 of the following criteria were defined as VAP:

- Fever (>38.5°C) or hypothermia (<36.5°C)
- Leukocytosis (leukocyte count >12,000/mm³), leukopenia (leukocyte count <4000/mm³)

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Lung imaging: Portable anterior-posterior chest X-rays taken in the ICU were evaluated for the presence of pneumonic infiltration by 2 chest diseases specialists. In the event of disagreement, the radiologist was consulted. No additional imaging was performed with lateral radiography or computed tomography (CT) for the radiological diagnosis of VAP or VAT.

Recorded information

Details of patient demographic characteristics, comorbidities, cause of ARF, arterial blood gas values, ratio of arterial oxygen partial pressure to inspired oxygen (PaO₂/FiO₂), chest radiography findings, intensive care severity scoring (Sequential Organ Failure Assessment [SOFA] score, Charlson Comorbidity Index score, Acute Physiology and Chronic Health Evaluation II [APACHE II] score), culture antibiogram results, treatment regimens, ICU hospitalization day, and mortality were recorded. The presence of mortality at 1, 2, 3, and 12 months of follow-up was documented using the national death records.

Statistical analysis

The IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) package program was used to perform the statistical analysis. Descriptive analysis was used to assess the demographic and clinical data of the study patients. Non-parametric continuous variables were evaluated with the Mann-Whitney U-test and the data were reported as median and interquartile ratio. Parametric tests

- Increased purulence of endotracheal secretions
  - VAP: VAT cases were defined as patients with at least 2 of the following criteria but no new or progressive infiltrate was observed on a chest radiograph:
    - Fever (>38.5°C) or hypothermia (<36.5°C)
    - Leukocytosis (leukocyte count >12,000/mm³), leukopenia (leukocyte count <4000/mm³)
    - Increased purulence of endotracheal secretions

Evaluation of the microbiological samples: Lower respiratory tract samples were collected 48 hours after mechanical ventilation and before the initiation of antibiotherapy via endotracheal aspiration or bronchial lavage with 5–10 mL 0.9% saline and the material was evaluated. A local anesthetic agent (lidocaine) was not applied to the bronchial system during bronchoscopy in order not to affect culture positivity. The samples were collected into a sterile polyethylene lavage tube. Cases in which dominant bacteria were detected in Gram staining and medium or intense growth was detected in a semi-quantitative culture, were accepted as indicating significant growth and cases with A. baumannii growth were included in the study. The 4-quadrant method was used to assess the semi-quantitative cultures. It was evaluated as 1+ (rare growth) if there was growth only in the first inoculation line, 2+ (light growth) if there was growth in the second inoculation line, 3+ (moderate growth) if there was growth in the third inoculation line, and 4+ (heavy growth) if there was growth in all areas.[21]
RESULTS

Of the 503 patients intubated during the study period, 78 patients who developed VAP or VAT due to A. baumannii were included in the study. Demographic characteristics, hospitalization and comorbidity details, cause of ARF, and the ICU severity scores of patients with VAP (n=28) and VAT (n=50) are compared in Table 1. The demographic characteristics and comorbidities were similar in the 2 groups. The presence of acute respiratory distress syndrome, the Charlson and SOFA scores, ICU and hospital stay duration data were also similar in the 2 groups (Table 2). Furthermore, there was no difference between the VAP and VAT groups in the occurrence of septic shock (p=0.551; Table 2).

ICU mortality was 67.9% in VAP cases and 40% in VAT cases (p<0.05; Table 2). There was no statistically significant difference between the groups in terms of long-term survival.

Figure 2. Kaplan-Meier cumulative survival analysis of ventilator-associated pneumonia and ventilator-associated tracheobronchitis groups.

were used for uniformly distributed values, and Student’s t-test was used to report continuous variables as the mean and SD. A chi-square test was used for binary variables such as female/male and presence/absence of additional disease. Number and percentage values were used where necessary. The Kaplan-Meier survival test was used for survival analysis. P<0.05 was considered statistically significant.
mortality (p>0.57; Table 2). The mean duration of mechanical ventilator use was 14.58 days (7–22 days) in the VAP group and 11.75 days (6–14 days) in the VAT group (p=0.05). The median follow-up period after discharge was 407 days (34–574 days) for VAT patients (n=30) and 112 days (34–524 days) for VAP patients (n=9) (Table 2).

Kaplan-Meier survival analysis results were similar for both groups (p=0.57, Fig. 2). The 1-, 2-, 3-, and 12-month mortality in VAT and VAP patients was 11.1% and 16.6% (p=0.69), 44.4%, and 26.7% (p=0.31), 44.4% and 33.3% (p=0.54), and 66.7% and 46.7%, respectively (p=0.29).

**DISCUSSION**

In our study, the ICU mortality rate of VAP patients with *A. baumannii* was significantly higher than that of VAT patients treated for the same cause; however, the mortality rate was similar during long-term follow-up of VAP and VAT patients.

In a multicenter study conducted by Nseir et al.,[18] which examined the effect of antibiotic treatment on VAP cases, the development of VAP and ICU mortality was significantly lower in the 8-day systemic antibiotic group compared with the non-antibiotic group (13%, 18% in the treatment group and 47%, 47% in the control group, respectively) and the study was terminated early due to the significant difference. It was reported in an observational prospective study that the most important factor preventing the conversion of VAT to VAP was the use of appropriate antibiotics.[19] Prevention of conversion of VAT to VAP with antibiotic treatment was found to be a positive result, but it was also demonstrated that it did not reduce mortality.[19] In the multi-center TAVeM (Incidence and prognosis of ventilator-associated tracheobronchitis) study conducted by Martin-Loeches et al.[20] VAT cases with and without appropriate antibiotic therapy were examined. The results indicated that there were fewer instances of conversion to VAP; the duration of mechanical ventilator use and ICU stay was reduced, and the mortality rate was lower in the treated VAT cases. In our study, when VAP and VAT patients were evaluated in terms of ICU mortality, the rate of VAP patients was found to be significantly greater however, mortality was similar in both groups in the long-term follow-up results. The duration of ICU stay and ventilator use of our VAP and VAT cases was similar to the results of the TAVeM study. In the case-control study performed by Nseir et al.,[18] it was found that the duration of mechanical ventilation and ICU stay was longer in patients with chronic obstructive pulmonary disease who developed VAT. Karvouniaris et al.[24] compared VAT cases (18%) with VAP cases and non-ventilator-related infections, and reported prolonged duration of mechanical ventilator and day of ICU stay in VAT cases (16 days [12–28 days], 27 days [15.7–43.5 days], 8 days [4–23 days], and 21 days [15–36 days], 30.5 days [16.75–45.25 days], 11 days [5.75–26 days], respectively). Our results revealed a shorter length of time on a mechanical ventilator and in the ICU: 11.75 days (6–14 days) in the VAT group, 14.58 days (7–22 days) in the VAP group, and 17 days (10–22 days) in the VAP group and 20 days (10–28 days) in the VAT group, respectively.

The incidence of VAT varies in the literature. While Roquilly et al.[25] reported an incidence of 5%, the rate was 11% in the TAVeM study[20] and 18% in a study conducted by Karvouniaris et al.[24] In our study, the incidence of VAT was 9.94%. The difference between these rates can be attributed to the fact that the diagnostic criteria for VAT are not the same and that a chest radiography is not sufficient to differentiate tracheobronchitis from pneumonia. We believe that VAT rates are likely affected by the differences in culture criteria/ICU protocols. In our study, chest radiography was used as the imaging method. Although it is thought that ultrasound and/or CT can provide a more detailed diagnosis in VAP and VAT cases, a radiological diagnosis can be more accurate. In addition, the transfer of ICU patients is not practical and the possibility of VAP/VAT may increase due to lack of head elevation during the imaging.

Noninvasive techniques are typically preferred for microbiological confirmation in intensive care practice. Ruiz et al.[25] found that endotracheal aspirate (ETA) culture samples had the same diagnostic value as other methods. In our study, only 5/78 of VAP and VAT patients were cultured with bronchial lavage and ETA was used in the remaining cases. There is no consensus on the ideal culture sample and the method to be used in the microbiological diagnosis of VAT.

As stated in the guidelines, mortality in the presence of septic shock and the possibility of multidrug-resistant pathogens are high in VAP cases.[21] Kumar et al.[22] reported that delay in antibiotic treatment, especially in patients with septic shock, was associated with increased mortality. In a survey conducted by Al-Omari et al.,[22] more than 50% of the participants reported that they preferred to start empirical intravenous colistin in the presence of septic shock in late-onset VAP patients. In our study, intensive care mortality and septic shock rates were higher in VAP cases, although in other studies they were similar.

Studies on the use of inhaled antibiotic therapy and systemic antibiotherapy are inconsistent.[28,29] Korbila et al.[28] observed that systemic and inhaler treatment provided a better cure, but mortality did not change. In a recent randomized controlled trial, there was no better clinical improvement with combination therapy of Gram-negative bacteria.[29]

When long-term mortality was evaluated, Kaplan-Meier survival analysis did not reveal a significant difference between VAP and VAT cases. We assume that these patients have a long-term colonization of resistant *A. baumannii* strains, and the infection is more likely to occur when their immunity is suppressed for any reason. There are some limitations to our study. First, the study population consisted of cases of VAP and VAT due to re-
sistant A. baumannii strains in a single ICU, and it may not be appropriate to generalize the information obtained to all patients. However, the results of this research may be valuable for similar patients because the study patients were followed up with the same protocol by the same pulmonologists and intensive care physicians. Patients infected with multidrug-resistant agents were also consulted to the same infectious diseases specialist to achieve a standard treatment control. Secondly, in our study, microbiological evaluation of the cases was performed using a semi-quantitative culture, rather than a quantitative culture. Although most authors think that quantitative culture and Gram staining is a more objective and useful assessment method, the ideal method for culture evaluation is not yet known. A third limitation of our study was use of chest radiography as a radiographic examination to differentiate between VAT and VAP. In ICU conditions, chest radiography has little sensitivity in differentiating between VAT and VAP, but it is the most easily accessible imaging method. In the present study, chest X-rays were evaluated by 2 different pulmonologists and radiologists were consulted in cases where VAT and VAP could not be differentiated. Finally, the cause of death and detailed culture results of the patients who died in the long-term period could not be obtained in our study. We believe that this problem can be answered in the future with prospective studies that follow the progression of patients who are colonized with resistant A. baumannii strains.

CONCLUSION

In our study, the intensive care mortality was higher in VAP patients with A. baumannii compared with VAT patients, despite systemic and inhaler antibiotic treatment. Nearly half of the VAT patients died, despite treatment. Nonetheless, these results support the notion that mortality will be higher in VAT patients without treatment. Acinetobacter strains are among the resistant pathogens that are a challenge to intensive care units today, and the importance of this issue is increasing. We believe that the similar mortality rates in VAP and VAT cases in the long-term support the view that Acinetobacter colonization be accepted and treated as an “infection” in VAT patients.

It may be useful for clinicians to use markers that enable them to distinguish between infection and colonization with more objective criteria and to create a personalized treatment plan for these patient groups in daily practice. Because of the high mortality rates of patients with VAP and VAT, both after intensive care and discharge, it is recommended that they should be closely monitored and called for weekly and monthly visits.

Ethics Committee Approval

Approval was obtained from the hospital ethics committee (Date/No.: 08.08.2017/116.2017.007).

Informed Consent

Retrospective study.

Peers-review

Internally peer-reviewed.

Authorship Contributions


Conflict of Interest

None declared.

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Gereç ve Yöntem: Çalışma, geriye dönük gözlemelidir. Uzman respiratörlerin ve bakteriyolojistin güvenilirliği ve yetersizlikleri araştırılmıştır.


Anahtar Sözcükler: Acinetobacter baumanii, VIIP, mortalite, mortalite oranı, mortalite riski, mortalite riski faktörleri, mortalite ve mortalite oranı ilişkisi.