Individualized antibiotic therapy in patients with ventilator-associated pneumonia

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Abstract
The optimal duration of the treatment of ventilator-associated pneumonia (VAP) is still the subject of debate. While 1 week treatment has been reported as possibly sufficient, patients generally receive antibiotic therapy for 10 to 14 days. The purpose of our study was to investigate whether length of treatment in patients with VAP can be reduced with an individualized therapeutic strategy. The study was performed prospectively with patients diagnosed with VAP in our hospital’s intensive care units between 1 January and 31 December 2015. Duration of antibiotic therapy was determined with 5 day clinical evaluation according to previously established criteria. Patients were divided into two groups depending on length of treatment, short (7–10 days) and long treatment (>10 days). Nineteen patients received 7 to 10 day antibiotic therapy, and 30 received >10 day antibiotic therapy. Demographic and clinical characteristics, Glasgow Coma Scale score, CPIS and the PaO2/FiO2 ratio at the time of diagnosis of VAP were statistically similar between the two groups (P=0.05). A second VAP attack occurred post-treatment in three patients receiving short-term treatment and in four receiving long-term treatment (P=0.561). The numbers of antibiotic-free days were 15.6±6.2 in the short-term treatment group and 8.3±7.5 in the long-term group (P>0.0001). One of the patients receiving short-term treatment died within 28 days after treatment, and four of the patients receiving long-term treatment (P=0.348) did so. The most commonly observed micro-organisms in both groups were Acinetobacter baumannii and Pseudomonas aeruginosa. Short-term treatment can be administered in cases with early clinical and laboratory response started on VAP treatment by considering individual characteristics and monitoring fever, CPIS, the PaO2/FiO2 ratio, C-reactive protein and procalcitonin values.

INTRODUCTION
Ventilator-associated pneumonia (VAP) is one of the most common health service-related infections, with a prevalence of approximately 15% in intensive care unit (ICU) patients [1]. VAP has an adverse impact on patient morbidity and mortality [1–3]. Since early and appropriate treatment is effective in reducing mortality in VAP, diagnosis must be made as quickly as possible, and appropriate empiric antimicrobial therapy must be started once specimens needed to identify the agent have been collected [4, 5]. For ideal antibiotic use, after accurate diagnosis, the correct antibiotic must be administered via the appropriate route, in an effective dose, at optimal intervals and for the proper length of time. Information concerning the optimal duration of the treatment initiated is limited [4]. Patients generally receive antibiotic therapy for 10 to 14 days [4–6]. Conditions in which treatment is prolonged are also frequently encountered. Duration of antimicrobial therapy is a confusing issue for clinicians due to problems of resistance and toxicity [6]. Studies aimed at lowering the length of treatment report that a period of 1 week may be sufficient [7].

The purpose of this study was to determine whether length of treatment in patients with VAP can be shortened with an individualized therapeutic strategy.

METHODS
This study was performed prospectively between 1 January and 31 December 2015 at the Karadeniz Technical University Medical Faculty Hospital Anesthesia and Reanimation Department ICU, and Neurology and Neurosurgery ICU. Patients diagnosed with VAP, aged over 18 years and attached to a mechanical ventilator for at least 48 h were included. Diagnosis of VAP was based on the Centers for Disease Control and Prevention (CDC) criteria and Clinical Pulmonary Infection Score (CPIS) [8–10]. Patients’ demographic characteristics and clinical findings were recorded onto study forms. Identification and antimicrobial
sensitivity testing of the causative micro-organisms obtained from endotracheal aspirate cultures and blood cultures (Bactec 9240; Becton Dickinson) were performed using the automated Phoenix system (Becton Dickinson) and classical methods. Results were interpreted in accordance with central laboratory standard institute guidelines [11]. Patients were started on empiric antibiotic therapy following diagnosis of VAP. Length of treatment was determined based on patients’ first 5 day clinical assessments. Patients were divided into two groups depending on duration of treatment (long-term and short-term treatments). Treatment was administered for 7 to 10 days in the presence of the criteria listed below. These patients were enrolled in the short-term group. Treatment was administered for more than 10 days in the absence of any of these criteria, and these patients were enrolled in the long-term group.

**Short-term treatment criteria**

(1) Absence of previous pulmonary disease,
(2) Presence of diffuse or patch-type infiltration and absence of localized infiltration at pulmonary radiography,
(3) Antibiotic initiated empirically being sensitive to the micro-organism grown in culture,
(4) Clinical response to treatment in the first 3 days
   - Decreases in frequency and degree of fever,
   - No increase in C-reactive protein (CRP),
   - PaO₂/FiO₂ >240,
   - A decrease of at least two points in CPIS,
(5) Clinical response to treatment in the first 5 days
   - Absence of fever,
   - 50 % decrease in CRP,
   - PaO₂/FiO₂ >300,
   - CPIS <5,
(6) 5 day monitoring without fever.

Following treatment, patients were monitored for 28 days in terms of clinical response, complications, recurrence of infection, infection with resistant micro-organism and mortality. Length of hospitalization, length of mechanical ventilation and time without antibiotic were recorded.

**Statistical analysis**

Data from the study forms were transferred onto SSPS software. Conformity with normal distribution of data obtained by measurement was tested using the Kolmogorov–Smirnov test. The Student’s t-test was used in the analysis of normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Data obtained by measurement were expressed as mean±SD, and data were obtained by counting as numbers (%). Analysis was performed using the chi-square test. P<0.05 was regarded as statistically significant.

**RESULTS**

VAP developed in 60 patients. All patients were started on empiric antibiotic therapy. Eleven patients died while receiving antibiotic therapy. These patients were excluded from the study because they could not complete the treatment period. A total of 49 patients were evaluated. Nineteen patients received short-term antibiotic therapy, and 30 patients received long-term therapy. None of these were part of the group due for the short-term therapy at the first fifth day evaluation. Mean age in the patients receiving short-term treatment was 50.3±15.4 years, and mean duration of treatment was 8.6±1.0 days. Mean age in the patients receiving long-term treatment was 48.9±21.3 years, and mean duration of treatment was 15.3±2.4 days. At comparison of the two groups (short- and long-term treatments) at the time of diagnosis of VAP, Glasgow Coma Scale (GCS) score was 8.4±1.5 and 7.4±2.8 (P=0.136); CPIS, 7.2±0.6 and 7.7±1.1 (P=0.153); PaO₂/FiO₂, 245±46 and 252±59 (P=0.675); CRP, 10.6±7.0 and 17.7±8.7 (P=0.005); and body temperature, 38.6±0.6 ºC and 38.5±1.0 ºC, (P=0.793), respectively. On the third day of treatment, GCS was 8.7 ±1.7 and 7.4±2.2 (P=0.019); CPIS, 4.8±0.7 and 6.2±0.8 (P<0.0001); PaO₂/FiO₂, 295±36 and 250±60 (P=0.007); CRP, 8.3±5.4 and 20.9±9.4 (P<0.0001); and body temperature, 37.8±0.3 ºC and 38.3±0.9 ºC (P=0.018), respectively. On the fifth day of treatment, GCS was 9.1±1.6 and 7.9±2.4 (P=0.036); CPIS, 3.4±0.5 and 5.4±0.6 (P<0.0001); PaO₂/FiO₂, 356±35 and 275±47 (P<0.0001); CRP, 5.4±2.5 and 18.4±7.8 (P<0.0001); and body temperature, 37.1±0.3 ºC and 37.9±0.7 ºC (P<0.0001), respectively.

A second VAP attack occurred in three of the patients receiving short-term treatment during post-treatment monitoring and in four of the patients receiving long-term treatment (P=0.561). All these were evaluated as relapse infections. No other infection with resistant micro-organisms occurred in the patients receiving short-term therapy but occurred in five patients receiving long-term treatment. Four of these were bacteremia, and the fifth was urinary infection. The mean numbers of antibiotic-free days were 15.6±6.2 in the patients receiving short-term treatment and 8.3±7.5 in those receiving long-term treatment (P<0.0001). One of the patients in the short-term treatment group died after 28 days, and four of those in the long-term group (P=0.348). Patients’ demographic and clinical characteristics and laboratory findings are shown in Table 1.

Gram-negative micro-organisms were the agents identified in 17 of the patients receiving short-term treatment and *Staphylococcus aureus* in two. Gram-negative micro-organisms were the agents in 25 patients receiving long-term treatment and *Staphylococcus aureus* in five (Table 2). The most common micro-organisms in both groups were *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Patients in the short-term treatment group in whom *A. baumannii* and *P. aeruginosa* were the agents received treatment for 9 to 10 days, while those with other micro-organisms received treatment for 7 to 8 days. Carbapenem resistance was present in 81.3 % of *A. baumannii* strains and 43.8 % of *P. aeruginosa* strains, while all strains were sensitive to colistin.
and methicillin resistance in lactamase production and carbapenem resistance in laboratory characteristics. Examples of such resistance include carbapenem resistance of resistant micro-organisms and drug toxicities [12, 13].

Long-term use of antibiotics, one of the main classes of drug used in ICUs, is one of the principal causes of the emergence of resistant micro-organisms and drug toxicities [12, 13]. Examples of such resistance include carbapenem resistance in A. baumannii and P. aeruginosa, extended-spectrum β-lactamase production and carbapenem resistance in Enterobacteriaceae and methicillin resistance in S. aureus [12, 14]. The best means of reducing the emergence of resistant strains in ICUs is sensible use of antimicrobials [14, 15]. The use of guidelines in diagnosis and treatment, antimicrobial de-escalation, avoiding the treatment of colonizations, monitoring serum antimicrobial levels and determining the appropriate length of antibiotic therapy are all essential for that purpose [13].

No consensus has been achieved on the optimal length of antibiotic therapy in patients with VAP. Several studies, reviews and guidelines suggest that 7 to 8 days of treatment may be sufficient in the majority of patients with VAP [16–20]. However, a longer duration is recommended in VAP developing with non-fermenting Gram-negative bacilli [16, 20, 21]. Chastre et al. [16] compared 8 and 15 day treatment in patients with VAP and observed no difference in terms of mortality and recurring infection in any agents other than with non-fermenting Gram-negative micro-organisms. Similarly, Pugh et al. [18] reported that 7 to 8 day treatment was sufficient in VAP developing with micro-organisms other than non-fermenting Gram-negative bacilli. However, none of these studies investigated clinical response to treatment in the first 5 days. Our study concluded that antibiotics can be discontinued once fever-free status is achieved in patients responding early to treatment, irrespective of the micro-organism involved. A. baumannii and P. aeruginosa were the agents in 68.4% of our patient group, and these received 9 to 19 days of treatment. Cases in which other micro-organisms were involved were treated for 7 to 8 days. In agreement with the literature, these findings support the idea that treatment in cases involving non-fermenting Gram-negative micro-organisms should be slightly longer. However, they also show that there are no adverse consequences from treatment being stopped once the 5 day fever-free status is achieved.

Several studies have shown that prolongation of treatment does not prevent the occurrence of relapse infection [17, 21–23]. In our study, relapse infection rates were similar.
between patients receiving long- and short-term treatment. The risk of infection with resistant micro-organisms increases in patients receiving longer antimicrobial therapy [13]. Infections with micro-organisms also occurred after treatment in patients receiving long-term treatment in our study.

The numbers of antibiotic-free days in ICUs increase with short-term antibiotic therapy [16, 17, 23]. This also prevents colonizations and infections that may occur with resistant micro-organisms. Patients receiving short-term antibiotic therapy in our study also remained antibiotic free for long periods. Mechanical ventilation was stopped earlier among the patients in the short treatment group, and these were discharged from hospital earlier. However, the differences were not statistically significant. There was also no difference between the two groups in terms of mortality.

The most important problem in VAP is the inability to achieve early clinical response in the majority of cases. Early clinical response is only possible in cases which are diagnosed and started on appropriate treatment early. Patients must therefore be evaluated in terms of infection every day, morning and evening. For example, 8% mortality is reported to occur for every hour in which effective antimicrobial therapy is delayed in patients with septic shock [24]. This suggests that every hour of delay in providing effective antimicrobial therapy in VAP will also reduce the probability of achieving an early clinical response. Body temperature in the short-term treatment group patients 1 day before diagnosis of VAP was lower than that in the patients in the long-term treatment group. This also suggests that delayed diagnosis and treatment affected early clinical response. In order to achieve clinical response, it is essential to estimate that the agent micro-organism will be sensitive to the empiric antibiotic therapy started. For that purpose, it is essential to be aware of the ICU survival data and patients’ detailed histories and previous antibiotic therapy and to follow the guidelines very closely [25, 26]. Clinical parameters (body temperature, the PaO₂/FiO₂ ratio, CPIS, CRP and procalcitonin) must also be closely monitored [18, 20]. Third and fifth day results for these parameters must guide the clinician in terms of duration of treatment and any need for adjustment [18, 20, 27].

One issue we think it will be useful to discuss from the reader’s perspective is ventilator-associated tracheobronchitis (VAT). Readers may ask whether VAT was present in the patients diagnosed with VAP in the short treatment group. It is important to answer this question. Because of the absence of a gold standard in the diagnosis of VAT, the subject of which approach will provide the best results is still a controversial one [28]. CDC criteria and CPIS were used in planning our study. Patients incompatible with both algorithms were excluded from the study so they did not affect the results. VAP and VAT are two conditions, both characterized by high fever, mucopurulent bronchial secretions and leukocytosis. However, in contrast to VAP, VAT does not involve the pulmonary parenchyma. Nor does it cause radiographic pulmonary infiltrates, new rales, bronchial breath sounds, worsening oxygen requirements or a compromised PaO₂/FiO₂ ratio [29, 30]. The presence of pulmonary infiltration at radiography, a low PaO₂/FiO₂ ratio and high CPISs in all our patients support the diagnosis of VAP. The use of CDC criteria and CPIS together and a mean CPIS score greater than 7 in patients in both groups increased specificity in the diagnosis of VAP and obviated the presence of bias.

In conclusion, short-term treatment can be administered in patients started on VAP treatment and in whom clinical response is obtained with monitoring of body temperature, CPIS, the PaO₂/FiO₂ ratio, CRP and procalcitonin values. The parameters that need to be monitored in observing clinical response are the decrease in third day body temperature, CRP and procalcitonin; the improvement in the PaO₂/FiO₂ ratio; and the decrease in CPIS. If the anticipated improvement in these parameters is not achieved, diagnosis and treatment must be reviewed. If complete improvement in these parameters is achieved on the fifth day of treatment, early discontinuation must be considered, and length of treatment must be planned. These parameters must be monitored during treatment planning, and treatment must be re-assessed in the event of worsening in these values. With short-term treatment based on patients’ individual characteristics, antibiotic-free days in the ICU will increase, the risk of encountering resistant micro-organisms will decrease and early discontinuation of mechanical ventilation and departure from the ICU can be achieved. This will reduce the risk of morbidity and mortality and also lower costs.

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Conflicts of interest
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