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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.

Results: Of the cases included in our study, 70.5% were male, and 29.5% were female patients. Of the cases, 87.5% were followed in Anaesthesiology and Reanimation Intensive Care Unit. The most common modifiable risk factors are mechanical ventilation, antacid use, and the most common non-modifiable risk factors were the presence of trauma and a history of cardiovascular disease.

Conclusion: Ventilator-associated pneumonia is a clinical condition with high mortality and morbidity in intensive care units. Incidence and mortality of ventilator-associated pneumonia can be reduced through the implementation of some necessary policies for the prevention of ventilator-associated pneumonia and the practices for the reduction or elimination of modifiable risk factors.

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

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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 after 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: $\geq 10^5$ 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).

Table 1 Distribution of Patients According to İntensive Care Units

Distribution of Patients According to İntensive 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%

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.

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 %	Older age	46	41.1%
Antacid use	112	100 %	Trauma	34	30.4%
Ng probe apply	102	91 %	Cardiovascular disease history	33	29.5%
Blood product support (more than >2 units)	51	45.5 %	Malignancy	22	19.6%
Tracheostomy	43	38.4 %	COPD	20	17.9%
Urinary catheter apply	109	98 %	DM	20	17.9%
İmmunosuppressive 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	Albümin	2.2	mg/dL
Platelet	230.000	µL	Procalcitonin (examined at 77of cases)	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

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.[7] 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.[8] Ventilator-associated pneumonia is a critical problem that causes prolonged stay in ICUs and hospital, cost increase, increase in morbidity and mortality rates.[9]

Acinetobacter baumannii is a species frequently leading to severe infections, which is characterized by the highest antibiotic resistance.[4] The followings are among the known risk factors: prolonged hospital stay, mechanical ventilation, underlying diseases, invasive procedures, inadequate-inappropriate antibiotic treatment and surgical treatment.[10] *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.[10] *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.[11] 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.[12] Moreover, VAP development risk is higher than the other units because of the more top ventilator use rate in Anaesthesiology and Reanimation ICUs.[3] 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.[13] In a study by Bonten et al.,[14] the development risk of VAP was reported to increase

by 5.1 fold in cases older than 60 years. Bilici et al.,[7] 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.,[14] 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.[7] 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%.[9] 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.[15] 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.[16] In a study by Öcal et al.,[17] 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.[18] Taşbakan et al.,[19] 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.[20] 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.[21] 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.,[22] 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.[23] 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.[24] Öcal et al.,[17] 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.[25] Chronic renal failure and heart failure are other risk factors for the development of VAP. In a study by İbrahim et al.,[26] heart failure has been shown to be a risk factor for both VAP and mortality. Bilici et al.[7] 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.,[27] 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%.[28] 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.[29] In the present study, antibiotic resistance profile evaluation has revealed that there was only one case who was resistant to antibiotics, including colistin.

Treatment 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.[30] 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.

REFERENCES

1. Şafak B, Çiftçi İH, Kıyıldı N, Aktepe OC, Çetinkaya Z, Altındiş M. Ventilatör İlişkili Pnömoni Tanısında Endotrakeal Aspirat Kültürleri: 2004-2006 Yılları Sonuçları. *Ankem Derg*. 2007; 21(2): 81-5.
2. Bonten MJM, Gaillard CA, Ramsay G. The Pathogenesis of Nosocomial Pneumonia in Mechanically Ventilated Patients. In: Vincent JL (Ed). Yearbook of Intensive Care and Emergency Medicine; Berlin: Springer Verlag: 1995; 711.
3. Saltoğlu N. Ventilatör İlişkili Pnömoninin Önlenmesi ve Kontrolü. İÜCTF STEE, Hastane enfeksiyonları: korunma ve kontrol. *Sempozyum Dizisi* 2008; 60: 89103.
4. Giamarellou H, Antoniadou A, Kanellakopoulou K. Acinetobacter baumannii: a Universal Threat to Public Health?. *Int J Antimicrob Agents*. 2008; 32(2): 106-19.
5. Aktaş F. Gram-Negatif Bakterilerin Hastane İnfeksiyonlarındaki Rolü Ve Epidemiyolojisi. Ulusoy S, Leblebicioğlu H, Arman D. Önemli ve Sorunlu Gram Negatif Bakteri İnfeksiyonları" kitabı, Bilimsel Tıp Yayınevi, Ankara, 2004: s: 183-206.
6. Jang TN, lee SH, Huang CH, lee Cl, Chen WY. Risk Factors and İmpact of Nosocomial *Acinetobacter baumannii* Bloodstream İnfections in the Adult İntensive Care Unit: a Casecontrol Study. *J Hosp Infect*. 2009; 73: 143-50.
7. Bilici A, Karahocagil MK, Yapıcı K, Göktaş U, Yama G. et al. Ventilatör İlişkili Pnömoni Sıklığı Risk Faktörleri ve Etkenleri. *Van Tıp Dergisi*. 2012; 19 (4): 170-176.
8. Leblebicioğlu H, Rosenthal VD, Arıkan ÖA, Özgültekin A, Yalçın AN, Koksal I, et al. Device-Associated Hospital Acquired İnfection Rates İn Turkish İntensive Care Units. Findings of the International Nosocomial Infection Control Consotium (INCC). *J Hosp Infect*. 2007; 65: 251257.
9. Chastre J, Fagon JY. Ventilator-Associated Pneumonia. *Am J Respir Crit Care Med*. 2002; 165: 867-903.
10. Tünay H, Demirdal T, Demirtürk N. Acinetobacter Enfeksiyonlarında Dirençle İlgili Değişen Tanımlamalar ve Dirençte Güncel Durum. *Türk Mikrobiyol Cem Derg*. 2012; 42(4): 123-126.
11. Kılıç M. Demet Çalışmasının Yoğun Bakım Ünitesindeki Hastalarda Ventilatör Ilişkili Pnömoni Üzerine Etkisi. Uzmanlik tezi. Yüzüncü Yıl Üniversitesi, Van, 2017.
12. Palabiyik O, Isik Y, Cegin MB, Goktas U, Kati I. Efficiency of Hematocrit, Lymphocyte, C-Reactive Protein and Transferrin Levels in Predicting Mortality in İntensive Care Unit Patients: a 2-Year Retrospective Study. *Eur J Gen Med*. 2015; 12: 222-6.
13. Gupta A, Agrawal A, Mehrotra S, Singh A, Malik S, Khanna A. Incidence, Risk Stratification, Antibiogram of Pathogens İsolated and Clinical Outcome of Ventilator Associated Pneumonia. *Indian J Crit Care Med*. 2011; 15: 96-101.
14. Bonten MJM, Kollef MH, Hall JB. Risk Factors for Ventilator-Associated Pneumonia: From Epidemiology to Patient Management. *Health Care Epidemiol*. 2004; 38: 890-8.

15. Aygen B. Kan ve Kan Ürünleri ile Bulaşan İnfeksiyonlar. In: Doğanay M, Unal S, eds. Hastane İnfeksiyonları. Ankara: Bilimsel Tıp Yayınevi, 2003: 855-74.
16. Agarwal R, Gupta D, Ray P, et al. Epidemiology, Risk Factors and Outcome of Nosocomial İnfections in a Respiratory Intensive Care Unit in North India. *J Infect*. 2006; 53: 98-105.
17. Öcal N, Öcal R, Özer S, Taşkın G, Doğan D, et al. Ventilatör İlişkili Pnömonide Değiştirilemeyen Risk Faktörleri ve Radyolojik Skorlamanın Prognostik Değeri. *Yoğun Bakım Derg*. 2016; 7: 44-8.
18. Kantorova I, Svoboda P, Scheer P, et al. Stress Ulcer Prophylaxis in Critically İll Patients: a Randomized Controlled Trial. *Hepatogastroenterology*. 2004; 51: 757-761.
19. Taşbakan MS, Deniz S, Gürgün A, Başoğlu Ö, Bacakoğlu F. Solunumsal Yoğun Bakım Ünitesinde Mekanik Ventilasyon Uygulanan Olgularda Üst Gastro-İntestinal Sistem Kanamaları. *Ege Tıp Dergisi / Ege Journal of Medicine*. 2010; 49(3): 185-191.
20. Celis R, Torres A, Gatell JM, et al. Nosocomial Pneumonia: A Multivariate Analysis of Risk and Prognosis. *Chest*.1988; 93: 318-24.
21. Saltoğlu N. Ventilatör İlişkili Pnömoninin Önlenmesi Ve Kontrolü. Hastane Enfeksiyonları: Korunma ve Kontrol Sempozyum Dizisi. 2008; 60: s.89-103.
22. Kılıç M, Demirkıran H, Yüzkat N. Trakeostomili Hastalarda Ventilatör İlişkili Pnömoni Görülme Sıklığı: Prospektif Çalişma. In: Akça H, Eraslan M, Sansar MF, editörler. II. Uluslararası Multidisipliner Çalışmaları Kongresi; 4-5 Mayıs 2018; Adana-Türkiye: s.629.
23. Hatipoğlu ON. Hastane Kokenli Pnomoni Risk Faktorleri. In: Arman D, Ucan ES, eds. Hastane Kokenli Pnomoni ve Tedavisi. Ankara: Bilimsel Tıp Yayınevi, 2004: 13-20.
24. Lorente L, Lecuona M, Galvan R, et al. Periodically Changing Ventilator Circuits is not Necessary to Prevent Ventilator-Associated Pneumonia When a Heat and Moisture Exchanger is Used. *Infect Control Hosp Epidemiol*. 2004; 25: 1077 - 82.
25. Alp E, Guven M, Yıldız O, Aygen B, Voss A, Doganay M. Incidence, Risk Factors and Mortality of Nosocomial Pneumonia in İntensive Care Units: A Prospective Study. *Ann Clin Microbiol Antimicrob*. 2004; 3: 17.
26. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH. The Occurrence of Ventilator associated Pneumonia in a Community Hospital; Risk Factors and Clinical Outcomes. *Chest*. 2001; 120: 555-61.
27. Uslu M, Öztürk DB, Kuşçu K, Aslan V, Gürbüz Y, Tütüncü EE, et al. Yoğun Bakım Ünitesinde Yatan Hastalarda Ventilatörle İlişkili Pnömoni Gelişmesine Etki Eden Risk Faktörleri. *Klimik Dergisi*. 2010; 23: 83-8.
28. Yılmaz G, Çaylan R, Ulusoy H, Aydın K, Erciyes N, Köksal İ. Yoğun Bakım Ünitesinde İzlenen Ventilatörle İlişkili Pnömonilerin Değerlendirilmesi. *Yoğun Bakım Dergisi*. 2004; 4(2): 131-137.
29. Paterson DL. The Epidemiological Profile of İnfections with Multidrug-Resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis*. 2006; 43 (Suppl 2): 43-8.
30. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global Challenge of Multidrug-Resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2007; 51(10): 3471-84.