Ventilator-associated pneumonia in surgical emergency intensive care unit

Bulent M. Ertugrul, MD, Ayse Yildirim, MD, Pinar Ay, MD, Serkan Oncu, MD, Atahan Cagatay, MD, Nahit Cakar, MD, Cemalettin Ertekin, MD, Halit Ozsut, MD, Haluk Eraksoy, MD, Semra Calangu, MD.

ABSTRACT

Objectives: To investigate the incidence, risk factors and the etiology of ventilator-associated pneumonia (VAP) in surgical emergency intensive care unit (ICU) patients.

Methods: We conducted this prospective cohort study in the surgical emergency ICU of Istanbul Medical Faculty between December 1999 and May 2001. We included 100 mechanically ventilated patients in this study. We diagnosed VAP according to the current diagnostic criteria. We identified the etiology of VAP cases by both quantitative cultures of endotracheal aspiration and blood cultures. To analyze the predisposing factors for the development of VAP, we recorded the following variables: age, gender, acute physiology and chronic health evaluation (APACHE) II score, Glasgow coma scale (GCS), sequential organ failure assessment (SOFA) score, serum albumin level, duration of mechanical ventilation (MV) prior to the development of VAP, and underlying diseases.

Results: We determined the VAP incidence rate as 28%. We found the APACHE II score and the duration of MV to be statistically significant variables for the development of VAP. There were no significant differences regarding age, gender, GCS, SOFA score, albumin level, or underlying diseases for the development of VAP. The isolated bacteria among VAP cases were as follows: *Staphylococcus aureus* (n=12, 43%), *Acinetobacter spp*. (n=6, 21%), coagulase-negative *Staphylococci* (n=4, 15%), *Pseudomonas aeruginosa* (n=3, 10.7%) and *Klebsiella pneumoniae* (n=3, 10.7%).

Conclusions: Ventilator-associated pneumonia is a common infection, and certain interventions might affect the incidence of VAP. The ICU clinicians should be aware of the risk factors for VAP, which could prove useful in identifying patients at high risk for VAP, and modifying patient care to minimize the risk of VAP.

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Due to underlying serious diseases and invasive interventions, the risk of nosocomial infections in patients treated in the intensive care unit (ICU) are rather high. In ICUs, particularly in patients requiring mechanical ventilator support, ventilator associated pneumonia (VAP) is the most common nosocomial infection.[1,2] Ventilator associated pneumonia is a complication of intubation and mechanical ventilator support.[3,4] It complicates the course of 8-28% of the patients receiving mechanical ventilation (MV).[5,6] The endotracheal tube plays an important role in the development of VAP. The tube itself impairs the defense mechanisms in the upper respiratory tract. In addition, this tube, serves as a template to form a biofilm layer.[7] For this reason, the pneumonia incidence in intubated patients is increased 3-10

From the Department of Infectious Diseases and Clinical Microbiology (Ertugrul, Oncu), Adnan Menderes University Medical Faculty, Aydin, Department of Anesthesiology and Reanimation (Yildirim, Cakar), Istanbul University Istanbul Medical Faculty, Department of Public Health (Ay), Marmara University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, (Cagatay, Ozsut, Eraksoy, Calangu), and the Department of General Surgery (Ertekin), Istanbul, *Turkey.*

Address correspondence and reprint request to: Dr. Bulent M. Ertugrul, Department of Infectious Diseases and Clinical Microbiology, Adnan Menderes University Medical Faculty, Aydin 09100, *Turkey.* Tel. +90 (532) 6456621. Fax. +90 (256) 2120146. E-mail: bulentertugrul@hotmail.com

fold.[5,8,9] Reports state VAP to be an independent risk factor that increases the mortality. The mortality is 2-2.5 times higher in patients with VAP than patients requiring MV without pneumonia.[10] In addition, VAP also increases the length of hospitalization significantly.[3,10] Some of the independent risk factors for VAP are: age >60 years, medical treatments (administration of some medicine such as H_2 blockers, antacids, dopamine, dobutamine, barbiturates), acute physiology and chronic health evaluation (APACHE) II score >16, trauma/head injuries, and MV >2 days.[5,6,11] The predominant organisms responsible for infection are *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Enterobacteriaceae*, but etiologic agents widely differ according to the populations of patients in an ICU, duration of hospital stay, and prior antimicrobial therapy.[12] We conducted this study to evaluate the incidence, risk factors and etiology of VAP in an emergency surgical ICU.

Methods. This prospective cohort study was conducted in the surgical emergency ICU of Istanbul Medical Faculty between December 1999 and May 2001. All patients, mechanically ventilated for longer than 48 hours, were consecutively enrolled in the study. Patients with pneumonia or positive culture results of endotracheal aspirate (ETA) before mechanical ventilation (MV) were not included in the study population. Patients were mechanically ventilated (Servo 900 C® Siemens, Eleme, Sweden) after intubating by orotracheal intubation tube (Portex®, Kent, UK). A Europe Medical Macrovent Respiratory Circuit® (Rusch, Kermen-Germany) was used. Respiratory circuits and humidifiers and heat filters (SIMS Portex®, Kent-UK) were changed as clinically indicated. The ETA and blood cultures were collected from patients diagnosed as VAP. The diagnosis of VAP was defined as a new infiltrate on the chest radiography with 2 or more of the following criteria:[13-15] fever (> 38.3^{O}C) or hypothermia (< 36^{O}C), increase in the amount and purulence of tracheal secretion, white blood cell count >12 000/mm^3 or <4000/mm^3, significant decrease in PaO_2, count of microorganism in quantitative ETA culture >10^5 colony-forming units (cfu)/mL. All patients' age, gender, and underlying illnesses on admission to ICU were recorded. Glasgow coma scale (GCS), APACHE II score, sequential organ failure assessment (SOFA) score, and serum albumin levels were determined at the time of MV. Patients were followed up for the following 48 hours after MV was stopped.

Microbiological processing. The specimens were immediately processed in the laboratory. Pure ETA fluid (0.01 ml) was plated on 5% sheep blood agar, MacConkey agar, and Sabouraud dextrose agar. All cultures were incubated at 37^{O}C under aerobic atmosphere. Cultures were evaluated for growth 24-48 hours later. Microbiologically confirmed cases of VAP required the isolation of bacteria in significant quantities (>10^5 cfu/mL) from ETA samples. All isolated microorganisms were identified by standard laboratory methods.[16] The BacT/Alert® (Organon Teknika, Durham, NC) was used for detection of microbiological growth in the blood cultures. At least 2 blood culture bottles, revealing the same bacterial pathogen, were considered as bacteremia. Antimicrobial susceptibility tests were performed as indicated by NCCLS M2-A7 and M100-S11.[17,18]

Statistical analysis. The VAP incidence was calculated both in terms of cumulative and patient-time intensity. The cumulative incidence rate was calculated by dividing the number of patients with VAP by the number of total patients. The incidence density was determined by dividing VAP episodes by the total number of days at risk. Continuous variables were compared using Student's t test or, when inappropriate, the Mann-Whitney U-test was used. Chi-square statistics were used for categorical variables or, when inappropriate, Fisher exact test was used. Differences between groups were considered to be significant for variables yielding a p-value ≤ 0.05.

Results. The age of patients varied between 1-94 (mean $\pm$ SD, 39.5 $\pm$ 25.7). Of the patients, 71% were men and 29% were women. Underlying diseases of the patients are shown in **Table 1**. All of the patients were taking either H_2 blockers or antacids. The VAP incidence rate was 28% (every patient with VAP had only one episode) and density of the VAP incidence was 28.7 episodes per 1000 MV days. The VAP development duration varied between 3-24 days after MV (mean $\pm$ SD, 9.0 $\pm$ 4.6). The APACHE II and SOFA scores, GCS and albumin levels are presented in **Table 2.** There were no significant differences regarding age, gender, GCS, SOFA score, albumin level, or underlying diseases for the development of VAP. However, the APACHE II score and the duration of MV were found to be statistically significant. The APACHE II score was mean $\pm$ SD 13.1 $\pm$ 4.4 in the group without pneumonia and 15.1 $\pm$ 4.8 in the group with pneumonia (p=0.05) (**Figure 1**). When patients with MV for < 4 days were taken as a reference group, then MV duration longer than 4 days increased the VAP risk 4.81 fold (**Table 1**). The mortality rate was 29% for all the patients. It was 26.4% (n=19) for the patients without pneumonia and 35.7% (n=10) for the patients with pneumonia. While the MV duration was 17.3 $\pm$ 7.8 in patients with VAP,

Table 1 - The associations between the characteristics of patients and the development of VAP by univariate analysis.

Characteristics of patients	Number of patients at risk	Pneumonia n	(%)	RR	*P*-value
Age					
≤18	24	5	(20.8)	1.09	
19-64	55	19	(34.5)	1.82	>0.05
≥65	21	4	(19)	1	
Gender					
Female	29	9	(31)	1.16	>0.05
Male	71	19	(26.8)	1	
Duration of mechanical ventilation					
≥5 days	73	26	(35.6)	4.81	0.005
≤4 days	27	2	(7.4)	1	
Underlying diseases					
Trauma	57	18	(31.6)	1.26	
Abdominal operation	23	5	(21.7)	0.87	>0.05
Other*	20	5	(25)	1	

RR - Relative risk, VAP - ventilator associated pneumonia,
*Burns, acute pancreatitis, upper gastrointestinal bleeding, necrotizing fasciitis, larynx cancer, Mallory-Weiss syndrome

Table 2 - The relationships between pneumonia and APACHE II score, Glasgow coma scale, SOFA score and albumin level.

Characteristics of patients	All patients (n=100)	Patients with Pneumonia (n=28)	Patients without Pneumonia (n=72)	*P*-value
APACHE II score (mean ± SD)	13.6 ± 4.6	15.1 ± 4.8	13.1 ± 4.4	0.05
Glasgow coma scale (mean ± SD)	11.0 ± 3.6	10.3 ± 3.6	11.3 ± 3.5	>0.05
SOFA score (mean ± SD)	5.4 ± 2.1	5 ± 2.1	5.5 ± 2.1	>0.05
Albumin level (mean ± SD)	2.89 ± 0.68	2.95 ± 0.62	2.87 ± 0.70	>0.05

APACHE - acute physiology and chronic health evaluation, SOFA - sequential organ failure assessment,
SD - standard deviation

Table 3 - Endotracheal aspiration and blood culture results of 28 patients with pneumonia.

Causative bacteria	Number of patients	Positive blood culture
Staphylococcus aureus	**12**	**9**
MRSA	11	8
MSS*A*	1	1
MRCNS	4	4
Acinetobacter species	6	2
Pseudomonas aeruginosa	3	0
Klebsiella pneumoniae	3	1
Total	**28**	**16**

MRCNS - Methicillin resistant coagulase-negative *Staphylococcus,*
MRSA - Methicillin resistant *Staphylococcus aureus,*
MSS*A* - Methicillin sensitive *Staphylococcus aureus*

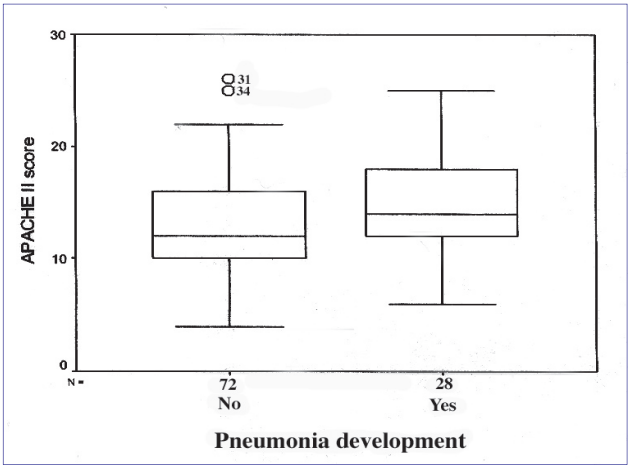

Figure 1 - The distribution of APACHE II score in the patients with and without pneumonia. Boxes illustrate the 25th and 75th percentiles; the lines inside the boxes represent the median value; "o" indicates values > 1.5-3 box-lengths from the end of the box.

it was 6.8 days ± 3.8 in patients without pneumonia. The isolated bacteria among VAP cases are shown in **Table 3**. All *Staphylococci*, except one, were resistant to methicillin. While the MV duration required for the development of VAP due to *Staphylococcus spp*. was 8.88 ± 3.77, it was 9.08 ± 5.6 for Gram-negative rods ($p>0.05$).

Discussion. Despite major advances in techniques for the management of ventilator-dependent patients, and the routine use of effective procedures to disinfect respiratory equipment, VAP continues to complicate the course of the patients receiving MV. Rates of pneumonia are considerably higher among patients hospitalized in ICUs compared with those in hospital wards, and the risk of pneumonia increases 3-10 fold for the intubated patients receiving MV.[5,6] The reported incidence of VAP in ICU patients varies widely, ranging from 9-70%.[19] Such wide variations might partly be attributable to the different patient populations studied however, studies using multivariate analysis have not found the type of patients to be an independent risk factor for the development of VAP.[19,20] Although, the incidence rate of VAP detected in our study (28%) was within reported ranges, the VAP incidence, detected as 28.7 episodes per 1000 MV days, was longer than in most previous studies.[5-21] In our study, we detected the mortality rate of patients with VAP as 35.7%, and without VAP as 24.4%. Prospective, randomized, controlled trials report similar outcomes for patients with VAP and without VAP.[22,23] Although the mortality rate was higher in patients with VAP, a statistical comparison could not be made between these 2 factors as matching could not be made according to the severity of the diseases. The mean duration of ICU stay prior to onset of pneumonia, which we detected as 9 days, was also consistent with prior studies.[5,14]

We found that the APACHE II score at ICU admission was a risk factor for VAP. However, we did not examine APACHE II score throughout the duration of MV as a potential risk factor for VAP. Many studies identify severity of illness as an important risk factor for VAP, which suggests that VAP can be decreased only to certain levels.[24-26] We also found that patients who developed VAP had longer MV duration than those who did not, which is consistent with other reports.[1,6,10,26,27] Although reports in previous studies state that age, underlying diseases (surgical patients are at high risk), low albumin level and GCS are the risk factors for VAP, the findings of this study are not consistent with those findings.[3,6,28] There were no significant differences regarding age (**Table 1**), however, the low incidence rate of VAP for age ≥ 65 years was striking. If 64 years of age was taken as a reference, the duration of MV was 10.5 days ± 7.3 in 79 patients whose ages were ≤ 64 years and 6.9 days ± 4.7 in 21 patients whose ages were ≥ 65 years ($p=0.02$). Therefore, there was a significant difference with regard to the duration of MV between the 2 groups. This might be the reason for the low VAP incidence in patients ≥ 65 years. But, on the other hand, although there was not a significant statistical difference, mortality rate was higher in patients ≥ 65 years. The mortality rate in patients ≥64 years was 26.6% (n=21) and 38.1% in patients ≥ 65 years (n=8).

In our study, we quantitatively evaluated ETA cultures in order to determine the etiological agents of VAP. The most important diagnostic means are cultures collected by protected brush method, bronchoalveolar lavage (BAL), or ETA. Quantitative ETA cultures are widely used instead of invasive diagnostic tests. This method is cheap and can be performed even by unspecialized laboratory personnel easily. On the other hand, it has a good correlation with bronchoscopic diagnostic methods.[9,29-31] Ruiz et al,[32] compared ETA and BAL for the microbiological diagnosis of VAP. Mortality, failure of initial treatment and the ICU length of stay were not significantly different in both methods. When Ionas et al,[33] compared BAL and ETA in terms of cost-effectiveness, a significant difference was found; BAL was 13-times more expensive than ETA. Therefore, we also prefer quantitative ETA culture for the diagnosis of VAP, as it is more practical and considerably cheaper.

In previous studies, the most frequently isolated bacteria from patients with VAP were Gram-negative rods.[11,29,34,35] But in this study, we found *Staphylococci* as the most frequently isolated bacteria. It is known that prolonged MV is a risk factor for infection with *Staphylococci*.[6] But in this study, although it was not significant, the duration of MV was longer for VAP cases caused by bacteria other than *Staphylococci*. The high rate of staphylococcal infection was especially associated with traumatized patients (64%) as reported in the work conducted by Artigas et al.[36] Frequent invasive intervention in this group of patients may explain the high rate of infection with this bacterium. One of the remarkable findings of our study was the frequent isolation of coagulase-negative *Staphylococci* (CNS) as the cause of VAP. The meaning of significant growth in quantitative cultures of CNS has been neither investigated in depth nor discussed in reviews or consensus conferences regarding VAP. As their virulence is low, we often consider CNS to indicate lung colonization or specimen contamination. However, there is ample evidence

that these bacteria can produce various infections in both immunocompetent and immunocompromised hosts.[37] Numerous studies have shown that critically ill patients have complex deficiencies in both cellular and humoral immunity.[38] Moreover, CNS has been found in lung cultures in post-mortem studies.[39] In some previous studies, CNS were also found to be the causative agent of VAP.[36,40]

In summary, we detected a high APACHE II score on admission to the ICU, and prolonged MV as risk factors for the development of VAP. *Staphylococci* were the most frequent etiological organism causing VAP. This finding concludes that we should include antibiotics effective against *Staphylococci* in the empirical treatment of VAP, especially in surgical ICUs where traumatized patient are in the majority. We detected CNS, generally perceived as commensals, as pathogens causing VAP.

References

1. Richardson CJ, Rodriguez JL. Identification of patients at highest risk for ventilator-associated pneumonia in the surgical intensive care unit. ***Am J Surg*** 2000; 179: 8-11.
2. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. ***JAMA*** 1995; 274: 639-644.
3. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. ***JAMA*** 1996; 275: 866-869.
4. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, et al. Effect of ventilator-associated pneumonia on mortality and morbidity. ***Am J Respir Crit Care Med*** 1996; 154: 91-97.
5. Craven DE, Steger KA. Epidemiology of nosocomial pneumonia. New perspectives on an old disease. ***Chest*** 1995; 108: 1S-16S.
6. Craven DE. Epidemiology of ventilator-associated pneumonia. ***Chest*** 2000; 117: 186S-187S.
7. Inglis TJ, Millar MR, Jones JG, Robinson DA. Tracheal tube biofilm as a source of bacterial colonization of the lung. ***J Clin Microbiol*** 1989; 27: 2014-2018.
8. National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986-April 1997, issued May 1997. A report from the NNIS System. ***Am J Infect Control*** 1997; 25: 477-487.
9. Grossman RF, Fein A. Evidence-based assessment of diagnostic tests for ventilator-associated pneumonia. Executive summary. ***Chest*** 2000; 117: 177S-181S.
10. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. ***Am J Med*** 1993; 94: 281-288.
11. Talon D, Mulin B, Rouget C, Bailly P, Thouverez M, Viel JF. Risks and routes for ventilator-associated pneumonia with Pseudomonas aeruginosa. ***Am J Respir Crit Care Med*** 1998; 157: 978-984.
12. Chastre J, Fagon JY. Ventilator-associated pneumonia. ***Am J Respir Crit Care Med*** 2002; 165: 867-903.
13. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. ***Am J Respir Crit Care Med*** 1996; 153: 1711-1725.
14. Garrard CS, A'Court CD. The diagnosis of pneumonia in the critically ill. ***Chest*** 1995; 108: 17S-25S.
15. Salata RA, Lederman MM, Shlaes DM, Jacobs MR, Eckstein E, Tweardy D, et al. Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. ***Am Rev Respir Dis*** 1987; 135: 426-432.
16. In: Ballow A, Hausler W, Herman K, Isenberg H, Shadomy I, editors. Manual of Clinical Microbiology. 5 ed. Washington DC: American Society for Microbiology; 1991.
17. Performance Standards for Antimicrobial Susceptibility Tests: Approved Standard. In: National Committee for Clinical Laboratory Standards. 7 ed. Wayne, Pa: NCCLS; 2000.
18. Performance Standards for Antimicrobial Susceptibility Testing; Eleventh Informational Supplement. NCCLS Document M100-S11. In: National Committee for Clinical Laboratory Standards. Wayne, PA: NCCLS; 2001.
19. Torres A, Aznar R, Gatell JM, Jimenez P, Gonzalez J, Ferrer A, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. ***Am Rev Respir Dis*** 1990; 142: 523-528.
20. Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. ***Intensive Care Med*** 1993; 19: 256-264.
21. Simsek S, Yurtseven N, Gercekogalu H, Izgi F, Sohtorik U, Canik S, et al. Ventilator-associated pneumonias in a cardiothoracic surgery centre postoperative intensive care unit. ***J Hosp Infect*** 2001; 47: 321-324.
22. Joshi N, Localio AR, Hamory BH. A predictive risk index for nosocomial pneumonia in the intensive care unit. ***Am J Med*** 1992; 93: 135-142.
23. Bregeon F, Ciais V, Carret V, Gregoire R, Saux P, Gainnier M, et al. Is ventilator-associated pneumonia an independent risk factor for death? ***Anesthesiology*** 2001; 94: 554-560.
24. Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. ***JAMA*** 1993; 270: 1965-1970.
25. Rodriguez JL, Gibbons KJ, Bitzer LG, Dechert RE, Steinberg SM, Flint LM. Pneumonia: incidence, risk factors, and outcome in injured patients. ***J Trauma*** 1991; 31: 907-912; discussion 912-904.
26. Sofianou DC, Constandinidis TC, Yannacou M, Anastasiou H, Sofianos E. Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. ***Eur J Clin Microbiol Infect Dis*** 2000; 19: 460-463.
27. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. ***Ann Intern Med*** 1998; 129: 433-440.
28. Mayhall CG. Nosocomial pneumonia. Diagnosis and prevention. ***Infect Dis Clin North Am*** 1997; 11: 427-457.
29. Bergmans DC, Bonten MJ, De Leeuw PW, Stobberingh EE. Reproducibility of quantitative cultures of endotracheal aspirates from mechanically ventilated patients. ***J Clin Microbiol*** 1997; 35: 796-798.
30. Torres A, Gonzalez J, Ferrer M. Evaluation of the available invasive and non-invasive techniques for diagnosing nosocomial pneumonias in mechanically ventilated patients. ***Intensive Care Med*** 1991; 17: 439-448.

31. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, El-Ebiary M, Carrillo A, Ruiz J, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. ***Am J Respir Crit Care Med*** 1998; 157: 371-376.
32. Ruiz M, Torres A, Ewig S, Marcos MA, Alcon A, Lledo R, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. ***Am J Respir Crit Care Med*** 2000; 162: 119-125.
33. Ioanas M, Ferrer R, Angrill J, Ferrer M, Torres A. Microbial investigation in ventilator-associated pneumonia. ***Eur Respir J*** 2001; 17: 791-801.
34. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. ***Am J Respir Crit Care Med*** 1999; 160: 608-613.
35. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. ***Am J Respir Crit Care Med*** 1998; 157: 531-539.
36. Tejada Artigas A, Bello Dronda S, Chacon Valles E, Munoz Marco J, Villuendas Uson MC, Figueras P, et al. Risk factors for nosocomial pneumonia in critically ill trauma patients. ***Crit Care Med*** 2001; 29: 304-309.
37. Kloos WE, Bannerman TL. Update on clinical significance of coagulase-negative staphylococci. ***Clin Microbiol Rev*** 1994; 7: 117-140.
38. Oberholzer A, Oberholzer C, Moldawer LL. Cytokine signaling--regulation of the immune response in normal and critically ill states. ***Crit Care Med*** 2000; 28: N3-12.
39. Kirtland SH, Corley DE, Winterbauer RH, Springmeyer SC, Casey KR, Hampson NB, et al. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. ***Chest*** 1997; 112: 445-457.
40. Strausbaugh LJ. Nosocomial Respiratory Infections. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 5 ed. Pennsylvania: Churchill Livingstone; 2000. p. 3020-3039.