SHORT-COURSE VERSUS LONG-COURSE ANTIBIOTIC THERAPY FOR VENTILATOR ASSOCIATED PNEUMONIA A RANDOMIZED TRIAL

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Abstract

Background: Ventilator-associated pneumonia is the most frequent ICU-acquired infection among patients receiving mechanical ventilation .The optimal duration of antimicrobial treatment for it is unknown. Shortening the length of treatment may help to contain the emergence of multi-resistant bacteria in the intensive care unit (ICU).

Aim of work: To evaluate the effects of short-course (eight days) versus long-course (fifteen days) antibiotics therapy among patients who acquired ventilator-associated pneumonia

Patients and Methods: Prospective randomized comparative cohort study was conducted on 60 patients of both sexes admitted to general ICU in the Alexandria Main University Hospital who had ventilator associated pneumonia based on Center of Disease Control criteria. The patients were randomized to 2 equal groups .Group A: was treated for only eight days and Group B: treated for fifteen day. The management was standardized according to ATS/IDSA guidelines.

Results: Compared with patients treated for 15 days, those treated for 8 days had neither difference in mortality (23.3% vs23.3%) no more recurrent infections (30.0vs 33.3%).The days of mechanical ventilation and the length of ICU stay in days for the 2 groups did not differ (13.07±2.39 vs. 14.53 ± 3.88) and (18.06±3.98 vs. 19.97 ± 4.16) respectively .But Group A had more mean antibiotic-free days(13.80 ± 7.56vs 9.50 ± 5.34)

Conclusion: We observed no benefit to prolong the antibiotics to 15 days regimen, for VAP patients whom received appropriate initial empiric antimicrobial treatment, as we found no differences in pulmonary infection recurrences and mortality.

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Introduction

The incidence of pneumonia acquired in the ICU ranges from 10% to 65 %.[1]Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide-range of preventive measures [2,3] .

VAP is defined as parenchymal lung infection occurring more than 48 hours after intubation and ventilation. VAP may be classified into; an-early onset which occurs within the first 4 days of hospitalization, usually carry a better prognosis, and is more likely to be caused by antibiotic sensitive bacteria, while late-onset VAP (5 days or more) is more likely to be caused by multidrug-resistant(MDR) pathogens like MRSA, Pseudomonas aeruginosa and Acinetobacter spp.[4]. The development of VAP prolongs the stay in the ICU and is associated with an increase in costs. It was found that the development of VAP was associated with an average of 4.3 days longer stay in the ICU than control subjects.[5].These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP.

All intensivists taking care of critically ill patients with severe infections must achieve the following two goals which may sometimes be difficult to combine: to treat the patient efficiently, quickly, and safely, on one hand; and on the other hand to avoid inappropriate and prolonged antibiotic therapies that could favour resistances.Hospitals and particularly intensive care units are faced with the emergence and rapid dissemination of multi-resistant bacteria, [6,7].In some cases, the choice of potential therapies is limited or even nonexistent[8]. The response to this challenge lies in a policy of prevention and better utilization of appropriate antimicrobial therapy, However, appropriate treatment includes not only the usage of an antimicrobial regimen with in vitro efficacy against the causal pathogen, but also the choice of the optimal dosage, route and duration of administration of this regimen shortening the duration and decreasing the number of antibiotics given to ICU patients to contain the emergence and dissemination of such pathogens. .Because of its frequency and severity nosocomial pneumonia in patients requiring prolonged mechanical ventilation represents one of the principal reasons for the prescription of antibiotics in the ICU[9]. We sought to gather and evaluate the currently available evidence regarding the optimal duration of anti-infective treatment for patients with VAP.

Aim of the work

To evaluate the effects of short-course (eight days) versus long-course (fifteen days) antibiotic therapy among patients who acquired VAP.

Patients

This Prospective randomized comparative cohort study was conducted on 60 patients (according to sample size calculation) of both sexes admitted to general ICU in the

Alexandria Main University Hospital from December 2013 to January 2015. The study was approved by the ethical committee of the faculty.

Inclusion Criteria

1.Age eighteen years or older

1. Mechanically ventilated and intubated patients with oral endotracheal tube or tracheostomy tube for more than 48h.
2. The patient diagnosed as having VAP during his stay in the ICU based on CDC criteria as follows:[10]

I-Radiological

One chest radiograph with at least **one** of the following:

- New or progressive and persistent infiltrate.
- Consolidation.
- Cavitations.

II-Signs/Symptoms/Laboratory

For any patient, at least **one** of the following:

- Fever (>38°C or >100.4°F) with no other recognized cause.
- Leucopenia (<4000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3).
- For adults >70 years old, altered mental status with no other recognized cause.

AND

At least **two** of the following:

- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements.
- New onset or worsening cough, or dyspnea , or tachypnea.
- Rales or bronchial breath sounds.
- Worsening gas exchange (e.g., PaO2/FiO2 < 240, increased oxygen requirements, or increased ventilator demand).

ExclusionCriteria

1. Patients with previous pulmonary disease, community acquired pneumonia and health care associated pneumonia.
2. Malignancy(on chemotherapy and or radiotherapy) and Immune-compromised patients
3. Patients have ARDS
4. Pregnancy.

Methods

Baseline Assessment and Data Collection

A written informed consent was obtained from the patient himself or the legal representative of the patient or his next of kin.

At admission to the ICU, we recorded each patient's age, sex, preexisting co-morbidities, severity of underlying medical condition(s) stratified according to APACHE II score.

- Microbiological investigations: Lower respiratory tract sampling, followed by microscopic analysis and culture of the specimen using either broncho-alveolar lavage (BAL) or a protected specimen brush (PSB)
- CPIS (The Clinical Pulmonary Infection Score)which was done for each patient on the 1st, 8th, and 15th days .(11)

Measurements (Patients monitoring)

All the patients included in the study were monitored through, clinical, radiological and laboratory findings:

- Clinical: Core body temperature every 8 hours, Blood pressure every day, Respiratory rate, Respiratory secretions (amount and color) as well as the number of suction need every 6 hours and efficiency of the gas exchange was evaluated daily through PaO2/FiO2 ratio and the minute ventilation.
- Laboratory and radiological : White blood cell count with differential count daily and chest X ray was done serially
- Final clinical outcomes: Days on the mechanical ventilator, ICU stay, hospital stay, 28- day antibiotic free days and 28- day mortality.

Study design

The study was randomized to 2 equal groups .Group A : Thirty patients were treated from VAP using the routine VAP treatment (empirical antibiotics based on American Thoracic society Guidelines for VAP treatment (12) followed by antibiotic modification guided by routine culture result) for only eight days . Group B: Thirty patients were treated from VAP by the routine VAP treatment for fifteen day.

Standard clinical management

Management of the patients with VAP was standardized according to ATS/IDSA guidelines. (12)

The period of the study was 8 days in group A (short course) and 15 days in group B(long course) starting from the diagnosis of VAP. the correlation of the results was done.

Statistical Analysis(13)

Data were collected, coded, tabulated then analyzed using SPSS computer software version 12.0. Numerical variables were firstly examined for normality then presented as mean and standard deviation (SD) . Between groups comparison of numerical variables was performed by unpaired Student-t test if they showed normal distribution, otherwise it was done using Mann-Whitney test.

Between groups comparison of categorical data was performed using Chi-square test or Fisher's exact test

Results

The two studied groups were matched in age, sex, reason of mechanical ventilation and other clinical characteristics at admission (Table 1).

Table 1: admission Characteristics of the studied patients

Characteristics	Short course group	Long course group	P value
Age(years),mean(SD)	56.70 ± 10.82	56.27 ± 10.07	0.873
Male, No. (%)	23 (76.7)	21(70.0)	0.559
Female, No. (%)	7(23.3)	9(30.0)	
Smoking, No.(%)	13 (43.3)	11 (36.8)	0.598
Reason for M.V,No.(%)			
• **Respiratory**	9 (30)	10 (33.3)	0.734
• **Cardiac**	5(16.7)	6 (20.0)	0.739
• **Neurological**	6 (20.0)	7 (23.3)	0.754
• **Others**	8 (26.6)	6 (20.0)	0.654
VAP Onset, mean(SD)	3.67 ± 1.37	3.77 ± 1.28	0.682
Early VAP ,No (%)	22 (73.3)	21 (70.0)	0.774
Late VAP, No(%)	8 (26.7)	9 (30)	
APACHE II score,mean(SD)	13.0 ± 2.62	14.40 ± 2.67	0.883

P is significant at ≤0.05

Micro- organisms considered responsible for VAP are listed in Table 2.The Staphylococcus aureus (either MSSA or MRSA) was the most common pathogen 26.7%,26.7% respectively while pseudomonas was the second cause with 23.3 % and 23.3%respectively.

Table 2: Etiology of Ventilator associated pneumonia

The Causative organism	Short course Group (n=30)		Long course Group (n=30)		P value
	No.	%	No.	%	
MRSA	5	16.7	5	16.7	0.0
MSSA	3	10.0	3	10.0	0.0
Psudomonas	7	23.3	7	23.3	0.0
Strept.pnemonia	3	10.0	3	10.0	0.0
Klebsilla	3	10.0	2	6.7	0.218
Acinetobacter	2	6.7	2	6.7	0.0
E.Choli	2	6.7	3	10.0	0.218
Enterobacter	2	6.7	2	6.7	0.0
Proteus	2	6.7	1	3.3	0.351
Haemophilus	1	3.3	2	6.7	0.351

P is significant at ≤0.05

None of the observed data as changes of Fever, Leukocytes count,Hypoxic index (PaO2/FiO2)and CPIS (Table 3) differed significantly between the two studied groups.

Table 3:Clinical variables in the two groups throughout the study

Clinical variables	Short course groups	Long course groups	P value
Temperature ,mean(SD)	37.40 ± 0.39	37.26 ± 0.61	0.293
Leukocyte count, mean(SD)	8.95 ± 3.91	8.43 ± 5.29	0.077
PaO2/FiO2 ,mean(SD)	334.27 ± 53.55	336.79 ± 59.86	0.865
CPIS ,mean(SD)	3.67 ± 2.41	3.72 ± 2.71	0.901

P is significant at ≤0.05

Outcome

Regarding the mortality ,twenty- eight days after VAP onset ,7 (23.3%) of 30 patients in the two studied group died (Table4).Based on culture results, the microbiologically documented pulmonary infection recurrence rate was 30.0% in short course group patients and 33.3 % in the long course one (Table 4).thus ,non inferiority of the short course therapy was retained .

In contrast, the patients who received antibiotics for 8 days had significantly higher mean antibiotic free days (13.80 ± 7.56 vs. 9.50 ± 5.34 days, P.004*).

There were no statistical significant differences between the two studied groups regarding the incidence of organ failure, the mechanical ventilation days and length of ICU stay. (Table 4)

Table 4: The outcome 28- days after VAP diagnosis

Outcome	Short course Group (n=30)		Long course Group (n=30)		P value
	No.	%	No.	%	
28-days Mortality	7	23.3	7	23.3	0.0
Pulmonary infection Recurrence (relapse ± super infection)	9	30.0	10	33.3	0.734
• **Relapse**	3	10.0	3	10.0	0.0
• **Super infection**	4	13.3	3	10.0	0.162
• **Combined**	2	6.7	4	13.3	0.145
Antibiotic free days , Mean (SD)	13.80 ± 7.56		9.50 ± 5.34		0.004*
ICU Stay, period in days Mean (SD)	18.06±3.98		19.97 ± 4.16		0.076
Mechanical ventilation days. Mean (SD)	13.07±2.39		14.53 ± 3.88		0.085
Organ failure	7	23.3	8	26.7	0.766

P is significant at ≤0.05

The most common causes of death was septic shock in the two groups with no statistical significant difference (Table 5)

Table 5: The causes of patients' death

Cause of death	Short course Group (n=30)		Long course Group (n=30)		P value
	No.	%	No.	%	
Septic Shock	4	57.1	3	42.9	3.447
Cardiogenic Shock	1	14.3	1	14.3	
Ventricular Arrhythmias	1	14.3	2	28.5	
Hepatic failure	1	14.3	0	0.0	
ARDS	0	0.0	1	14.3	

Statistically significant at p ≤ 0.05

Discussion

In this study we found that the two groups were matched together at admission ,regarding the age and sex with predominance of male gender .We were similar to Noyal et Al[14], and Jean Chastre et Al[15] who found no difference regarding the mean age between the two groups ,and also found that the male gender is predominant . The two studied groups were matched together regarding the cause of mechanical ventilation with agreement with Jean Chastre et Al [15],who also found that the respiratory causes were the most common.

There was no significant difference between the two studied groups regarding the duration of ventilation before VAP onset. The etiologic agents widely differ according to the population of patients in an intensive care unit, duration of hospital stay, and prior antimicrobial therapy [16]. Saroj Goliaet al.,[17]found that out of 148, mechanically ventilated patients only 52 patients were diagnosed as VAP cases based on clinical and microbiological grounds .Out of the 52 VAP cases, 23(44.23%) were categorized under early onset VAP and 29 (55.77%) under late onset VAP , 45(86.54%) were mono-microbial and 7 (13.46%) were poly-microbial .

Also in Noyal et Al [14], they found that the duration of MV and outcome of early onset and late onset VAP did not differ significantly. Late-onset VAP, caused by MDR pathogens was usually associated with increased morbidity and mortality.[18]

In agreement with Jean Chastre et Al, [15] the most common pathogen was the staphylococcus aureus (MSSA and MRSA)20.3%,19% respectively while pseudomonas was the second cause with 18.4 % and 19.6% respectively, also Gastmeier P ,et Al, [19], a study showed that gram positive cocci mainly Staphylococcus aureus and Streptococcus pneumonia were the most frequently isolated organism in early onset VAP which is in similar to our study .In contrast to our study, SarojGoliaet al., [17] found that Pseudomonas aeruginosa and E. coli were the commonest isolates obtained in both early and late onset VAP cases, as Pseudomonas aeruginosa was 33.3% in early onset and 34.9% in late onset VAP,which were also reported as the commonest isolates by other studies (Sharma et al.,[20] , Mukhopadhyay et al.,)[21]

The CPIS has been used to aid in the diagnosis of VAP. A total score >6 suggests VAP. Initially, the CPIS was validated in 40 quantitative cultures of bronchoalveolar lavage (BAL) fluid specimens from 28 patients. It has been identified that the most sensitive component of this score is, improvement of oxygenation.[22]

Despite of the wide range of long standing debate around the CPIS it is the only score that can be used in the section of HAP and VAP up to date. The clinical practice guidelines for HAP and VAP in adults from Canada, prepared jointly by the Association of Medical Microbiology and Infectious Disease Canada and the Canadian Thoracic Society [23], recommended the following:

1. The CPIS should be calculated to improve sensitivity and specificity for the diagnosis of HAP and VAP.

2. A low CPIS may allow careful observation of the patient without antibiotics.
3. By the third day of calculating the CPIS, a score < 6 may allow early discontinuation of antibiotics.

There was no statistically significant difference between the two groups when the CPIS was calculated on admission and in the last day of the study.In the current study, the CDC criteria for VAP were used rather than the CPIS as a tool of diagnosis [(10)]. The main use of CPIS in the study was to determine the short term outcome of the studied patients in the two groups and the effect of both short and long course antibiotic therapy in VAP management.

Microbial pathogens involved in VAP are frequently multidrug resistant (MDR), which challenges the appropriateness of empirical antibiotic prescription [(12)]. Several authors have observed increased mortality in VAP caused by MDR pathogens as compared with other bacterial pathogens, which they have attributed to a higher risk of initial inappropriate antibiotic therapy in these cases [(24-26)]. In our study we found that there was no statistical significant differences between the two studied groups regarding Multi-drug resistant micro-organisms (MDRS), the percentage in the 8 days group was(13.3%) and in 15 days group was 3 (10.0%). Combes A.et al,[(27)],found that The VAP recurrence rates, length of ICU stay and duration of mechanical ventilation did not differ for susceptible and resistant strains. While In Depuydt et al. [(28)], found that 30-day ICU and in-hospital mortality were significantly higher in patients with VAP caused by MDR organisms .

None of the observed data as changes of Fever, Leukocytecount,Hypoxic index (PaO2/FiO2), and CPIS differed significantly between the patients in the two studied groups.

We observed no benefit of prolonging antibiotic therapy in patients with VAP (microbiologically confirmed) who received appropriate initial empiric antimicrobial treatment, we found no differences in pulmonary infection recurrences and mortality between the two groups. Pulmonary infection recurrences either (Relapse, Super- infection and combined),did not differ significantly between the two groups .the pulmonary infection relapses were considered when there were re-appearance of signs of pneumonia and isolation of the same pathogen(s) that have acquired resistance or not, while super-infection considered if new pathogen(s) different from those encountered in the initial episode of VAP was isolated. In agreement with Jean Chastre ,et al.,[(15)]who found that the pulmonary infection recurrence rate was 28.9% of patients receiving the 8-day regimen and 26% of those taking antibiotics for 15 days with an absolute difference of 2.9%. Another study Erika J. et al, [(29)] found that, 48% of the studied patients had recurrent VAP. Sixty eight percent of recurrent episodes involved NF-GNB or MRSA. The median time to recurrence was 9 days. The majority of recurrences were due to super-infections, regardless of the organism isolated from the first episode ,also they found that no relationship between the microbiology of the first episode and the recurrence.

In our study we assessed the effect of short course (8 days) antibiotic therapy and the long course (15 days) and its impact on the outcome of ventilator associated pneumonia ,we found no statistical significant differences between the two studied groups regarding mechanical ventilation days, and ICU stay in days.

But we found statistical significant differences between the two studied groups regarding antibiotic free days. The mean of antibiotic free days in group A was 13.80 ± 7.56 while in group B the mean was 9.50 ± 5.34 significant differences between the two groups.

In agreement with our study, Jean Chastre ,et al.,[15]who found that no statistical significant differences regarding both mechanical ventilation free days ,length of ICU stay in days between the short and the long course group ,as mechanical ventilation free days were 8.7±9.1 and 9.1± 9.4 ,the length of ICU stay were30.0 ±20.0 and 27.5 ± 17.5 ,while the antibiotic free days were higher in short course group13.1 [7.4] vs 8.7 [5.2] day in the long course one.

Conclusion

Based on all the previous data and the results of the current study, we concluded that shorting the duration of the antimicrobial therapy for VAP increase the antibiotic free days and decreasing the unnecessary exposure to different antibiotic which have a direct effect on emerging MDR micro-organism without any benefit on the mortality and unfavorable outcomes.

References

1-Eggimann P, Pittet D. Infection control in the ICU. Chest. 2001;120(6):2059-93.

2.NiedermanMS.Guidelines for the management of respiratory infection: why do we need them, how should they be developed, and can they be useful? CurrOpinPulm Med 1999;2:161-5.

3.Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation.AmRevRespir Dis 1986; 133:792-6.

4.Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, Gibert C. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J RespirCrit Care Med 1998; 157:531-59.

5.Long MN, Wickstrom G, Grimes A, Benton CF, Belcher B, Stamm AM. Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. Infect Control Hosp Epidemiol. 1996 ;17(1):14-9.

6.Fridkin SK, Steward CD, Edwards JR. et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2: Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. Clin Infect Dis.1999;29:245

7.Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA.2003;289:885-88.

8.Mahgoub S, Ahmed J, Glatt AE. Completely resistant Acinetobacterbaumannii strains. Infect Control Hosp Epidemiol.2002;23:477-84.

9.Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. JAMA.1996;275:866-69.

10.CDC guidelines Ventilator-Associated Pneumonia (VAP) Event [database on the Internet]2008.Availablefrom:http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf

11.Zilberberg MD, Shorr AF. Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. Clin Infect Dis. 2010 ;51 (1):131-5.

12.Michael S, Donald E, Marc J, Jean C, William A, Jean-Yves F, et al. Guidelines for themanagement of adults with hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Am J Respir Crit Care Med. 2005;171(4):388-416.

13.Kirkpatrick L, Feeney B. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif: Wadsworth, Cengage Learning; 2013.

14. Mariya Joseph N, Sistla S, Kumar Dutta T, Shankar Badhe ,et.al.Outcome of ventilator-associated pneumonia.2012;5(2):135-40.

15. Jean Chastre ,Michel Wollf,Jean Y,et.al.Comparison of 8vs15 Days of antibiotic therapy for VAP in adults.2003;219(19).

16. Centers for Disease Control and Prevention. Monitoring hospitalacquired infections to promote patient safety: United States,.MMWR2000;49:149-53.

17. Saroj Golia1, Sangeetha K.T.1, Vasudha C.L:Microbial Profile of Early and Late Onset Ventilator Associated Pneumonia in The Intensive Care Unit of A Tertiary Care Hospital in Bangalore, India. 2013;7(11):2462-66.

18. Niederman MS, Craven DE..Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J RespirCrit Care Med. 2005;171(416):388.

19. Gastmeier P, Sohr D, Geffers C, Ruden H, Vonberg RP, Welte T, Early- and Late-Onset Pneumonia: Is This Still a Useful Classification? Antimicrob Agents Chemother 2009 July; 53(7):2714-18.

20. Sharma P.C, Raut S.S, More S.R, Rathod V.S, Gujar V.M, J of evolution of med and dental sci 2012; 1(3):192-7.

21.Mukhopadhyay C, Bhargava A, Ayyagari A, Role of mechanical ventilation and development of multidrug resistant organisms in hospital acquired pneumonia Indian J Med Res 2003; 118:229-35.

22.Napolitano LM. Use of severity scoring and stratification factors in clinical trials of hospital-acquired and ventilator-associated pneumonia. Clin Infect Dis. 2010 ;51 (1):S67-80.

23. Rotstein C, Evans G, Born A, Grossman R, Light RB, Magder S, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. Can J Infect Dis Med Microbiol. 2008 ;19(1):19-53.

24.Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest. 1999 ;115(2):462-74.

25. Alvarez-Lerma F, Alvarez B, Luque P, Ruiz F, Dominguez-Roldan JM, et al.:Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. Crit Care 2006; 10:78.

26..Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D: Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis.Am J Med 2003; 115:529-35.

27. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J: Impact of piperacillin resistance on the outcome of Pseudomonas ventilator-associated pneumonia. Intensive Care Med 2006 ; 32:1970-78.

28.PieterODepuydt, Dominique M Vandijck, Maarten A Bekaert, Johan M Decruyenaere,Stijn I Blot, Dirk P Vogelaers : Determinants and impact of multidrug antibiotic resistance in pathogens causing ventilator-associated-pneumonia. Critical Care 2008; 12:142.

29. Erika J. Lu.Paul Succop, Erin Haynes : Factors associated with ventilator-associated pneumonia recurrence in the surgical intensive care unit, 2007.