

Etiology and Drug Resistance Pattern of Ventilator Associated Pneumonia in an Iranian 1000- bed Tertiary Care Hospital.

ABSTRACT

Background and Objectives: Ventilator associated pneumonia (VAP) is the most common nosocomial infection in ICUs and making up one-third of the total nosocomial infections. The aim of this study was to determine etiology and drug resistance pattern of most frequency isolates responsible for VAP an Iranian 1000-bed tertiary care hospital in Tehran Iran.

Methods: VAP was defined as any lower respiratory tract infection that developed 48 hours after mechanical ventilation. Tracheal aspirate Specimens were collected and processed according standard microbiological methods. Bacterial identification and susceptibility testing were performed using standard procedures as recommended by CLSI.

Results: One hundred and one patients developed at least one episode of nosocomial pneumonia were subject of our study. Of 101 patients 61 patients were male and 40 female patients. The mean time for hospitalization in ICUs and ventilation duration were 16 and 9, 5 days respectively. Old age, History of previous use of antibiotics and duration of ventilation times were the most important risk factors for VAP. In total 126 microorganisms were isolated from VAP cases. *Acinetobacter baumannii* with 46 (36.5%) isolates was the predominant organism followed by *Staphylococcus aureus* by 3 (24.6%). *Pseudomonas aeruginosa* was accounted 19 (15%) isolates. Other isolated organisms included *Klebsiella pneumoniae* and *E.coli*. The majority isolated organism included *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were resistant to many antibiotics including the third generation of cephalosporins and nearly 50 % isolates were resistant to Amikacin. Colistin was the most effective antibiotic against multidrug resistant (MDR) isolates. We found a high rate of methicillin resistant *Staphylococcus aureus* (93.54, %). All isolates of *S. aureus* were susceptible to vancomycin.

Conclusion: Our study revealed that *A. baumannii*, *S. aureus* and *P.aeruginosa* were the major etiological agents of VAP in our hospital. The majority isolates were resistant to routinely used antibiotics including the third generation of cephalosporins. We also observed a high rate of MRSA among our isolates.

Key Words: Ventilator Associated Pneumonia, Drug resistance

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring more than 48 hours after patients have been intubated and received mechanical ventilation [1]. The incidence of nosocomial pneumonia in ventilated patients especially in intensive care units (ICUs) is very high and ranging from 7% to more 40%. Such nosocomial infections prolong hospital stay and causes patients' mortality [2, 3]. In the ICUs, the risk of mortality appears to be 2 to 10 fold higher in patients with nosocomial pneumonia than those patients without. In addition investigators have reported that nosocomial pneumonia increased the duration of hospitalized patients two fold to threefold compare to patients without nosocomial pneumonia [4]. In spite of remarkable progress in diagnosis and treatment of ventilator associated pneumonia over the recent years, conflicts persists over the optimal methods for diagnosis of VAP applying conventional laboratory methods is critical for identifying specific etiologic agents, for establishing appropriate treatment protocols [3, 4].

There are still not well accepted gold standards for diagnosis of VAP, but rather there are some diagnosis methods with different sensitivity and specificity [6, 7]. Nonbronchoscopic methods, such as blinded bronchoalveolar lavage (BAL) or quantitative endotracheal aspiration, along clinical signs, are more specific than only clinical diagnosis. Other methods such as bronchoscopic methods for obtaining BAL or a protected specimen brushing (SPS) has a higher specificity also than a clinical diagnosis. (8,9) However regardless of diagnostic method used, the American Thoracic Society Consensus group surest empirical initially therapy, based on the severity of the patients disease and the stage of onset, using antibiotics to cover common pathogens and patient's specific risk factors [3,4].

The bacteriologic diagnosis of VAP is still a controversial issue. This challenges in microbiology due to differentiation of between organisms responsible for the infection and colonizing normal flora. As motioned above there are many techniques for specimen collection to determine the true etiological agents. Also some techniques such as bronchoscopic are recommended as a gold standard methods; however some researchers have argued against routine use of these techniques and have suggested empiric therapy or less invasive techniques such as tracheal aspiration which is more cost effective approaches in clinical practice [4, 5,6,7,8,9,].

The aim of this study was to determine etiologic agents of VAP in patients hospitalized in an Iranian 1000-bed tertiary care hospital. Our other objective was detection antimicrobial susceptibility pattern of isolated microorganism to improve antibiotic strategy policy in our hospital.

MATERIALS AND METHODS.

This prospective study was performed in ICUs of Milad hospital. Milad Hospital is a 1000-bed non-teaching social security hospital. This hospital has an infection control system supervised by the infection control committee of the hospital.

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VAP was defined as any lower respiratory tract infections that developed after 2 day of mechanical ventilation. The criteria for clinical suspicion of nosocomial pneumonia included being new or present lung opacity on chest X-ray in addition two of the following items. (1) Fever 38.3C or (2) WBC counts 10000 or 5000 (3) purulent endotracheal aspirate. f patients in whom VAP was suspected, a deep tracheal aspiration with quantitative culture performed within 6 hours after the development of a new pulmonary infiltrate. Briefly after the tracheal aspiration collection, it was

transferred into vials containing 1 ml of sterile lactate Ringers solution .The vial was vigorously agitated for at least 60s to suspend all the materials from the aspirate. Specimens were immediately sent to the microbiology laboratory for quantitative cultures. 0.01 ml of specimen were taken from the original suspension and inoculated in Blood agar, Chocolate agar, Mac Conkey agar, and Sabouro dextrose agar. All culture plates were incubated at 37C for 24 hours Chocolate agar plate was incubated 10% Co2. All microorganisms were identified by conventional microbiological methods. Bacterial counts of 10⁵ CFU/ml or greater were used as the cutoff point for the diagnosis of VAP [10, 11, 12].

Microorganisms susceptibility testing was performed using guideline recommended by Clinical laboratory standard institute (13). Results of susceptibility testing expressed as percentage of susceptible, intermediate or resistant .Demographic data of patients including age, sex history of previous antimicrobial therapy, mechanical ventilation duration abstracted from the patient's file.

RESULTS

One hundred and one patients developed at least one episode of nosocomial pneumonia. Of 101 patients 61 patients were male and 40 female. The mean time for hospitalization in ICUs and ventilation were 16 and 9, 5 days respectively.

Old age, history of previous use of antibiotics and duration of ventilation times were the most important risk factors for VAP accusation. In total 126 microorganisms were isolated from VAP cases. *Acinetobacter baumannii* with 46 (36.5%) isolates was the predominant organism followed by *Staphylococcus aureus* by 31 (24.6%). *Pseudomonas aeruginosa* was accounted 19 (15.7%) isolates .Other isolated organisms were *Klebsiella pneumoniae* , *E.coli* and other miselinous gram negative organisms. We have also one isolates of *Candida albicans*. The majority organism including *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were resistant to many antibiotics including the third generation of cephalosporin's and aminoglycosides. Nearly 50% isolates were resistant to amikacin. Colistin was the most effective antibiotic against multidrug resistant (MDR) isolates. We found a high rate of methicillin resistant *Staphylococcus aureus* (MRSA) in our study 93.54, % isolates were MRSA. All isolates of *S.aureus* were susceptible to vancomycin .

DISCUSSION

Ventilator –associated pneumonia continues to be the most common nosocomial infections in ICU hospitalized patients and accounted nearly one third of the total nosocomial infections .Patients with VAP have worse outcomes and longer hospital stay and a mortality rate of 15 to 50%. In addition ICU inpatients with VAP increased by a mean of 6.1 days and a high excess cost. [14] A wide variety of pathogenic organisms are etiologic agents of VAP In the management of VAP specific antimicrobial therapy should be directed at the pathogen involved in each patient. Use of microbiology methods is an attempt to determine etiologic agent of VAP cases [10].The distal airways become colonized a few hours after intubation and nearly 10 microorganisms are recovered in ventilated patients. Because of their peculiar antibiotic resistance patterns methicillin resistant *S .aureus*, *P. aeruginosa* and *Acinetobacter baumannii* should be considered in the initial decision in the choice of antimicrobial therapy. Many studies have shown that these three organisms are the leading cause of death owing to VAP [14, 15, 16, 17, 18, 19]. Gram- negative bacilli accounted for more than 75% of isolates and predominant microorganisms were *Klebsiella pneumoniae*, *Pseudomonas*

aeruginosa, and *Acinetobacter* species. *Staphylococcus aureus* predominant gram- positive bacterium isolate. . In A study from Brazil the microbiological profile associated with VAP.were *A.baumani*(28%) *P.aeruginosa* (19%) and *S.aureus* 20%

156 respectively [23]

157 The prevalence of multidrug-resistant (MDR) organisms has increased over the past
 158 decade and a significant rise in these isolates in VAP has been observed. MDR seems
 159 to cause major early mortality and an adequate therapy is essential to treat VAP. [24]
 160 .In our study the majority isolates of *P.aeruginosa* and *A.baumannii* were MDR and
 161 resistant to third generation of cephalosporins was prevalent and also %84.78 isolates
 162 were resistant to imipenem. With the increase in resistance to carbapenems, colistin
 163 has been extensively used, however some data suggest that the doses recommended
 164 are insufficient before a steady state reached, suggesting that the administration of a
 165 loading dose on initiation of treatment may be beneficial. Combinations of
 166 antibacterial agents such as imipenem plus sulbactam or imipenem plus colistin have
 167 been successfully used to treat VAP [25].In our study colistin was the most effective
 168 antibiotic against *A.baumannii* isolates. Among gram- positive cocci MRSA was an
 169 important causative agent of VAP. Treatment of VAP caused by MRSA associated
 170 with poor outcomes in comparison with MSSA. In our study nearly all isolates were
 171 MRSA and vancomycin was the most effective antibiotic against MRSA isolates.

172 Our study had some limitation and did not allow a complete analysis of all risk
 173 factors responsible in VAP and MDR organisms. There are also more studies needed
 174 to be done in our country to compare the occurrence of VAP and community
 175 acquired pneumonia .We also needed a cooperation between physicians for
 176 providing clinical data and best qualified performance ,of laboratory practice.
 177

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Table -1 prevalence of etiologic agents of VAP

Organism	No (%)
<i>Acinetobacter baumannii</i>	46(36.5)
<i>Staphylococcus auerus</i>	19(24.6)
<i>Pseudomonas aeruginosa</i>	19(15.07)
<i>E.coli</i>	9(7.14)
<i>Klebsiella pneumoniae</i>	9(7.14)
<i>Stenotrophomonas maltophilia</i>	4(3.17)
<i>Klebseilla planticola</i>	4(3.17)
<i>Enterobacter cloacae</i>	1(0.79)
<i>Bukerderia cepaciae</i>	1(0.79)
<i>Proteus mirabilis</i>	1(0.79)
<i>Candida albicans</i>	1(0.79)
Total	126(100)

Table 2- Prevalence of Drug resistance among *Acinetobacter baumannii* isolates from

Antibiotic	Susceptible	Intermediate	Resistant
Cefotaxim	0(0.00)	0(0.00)	46(100)
Ceftizoxim	0(0.00)	0(0.00)	46(100)
Ceftazidim	0(0.00)	0(0.00)	46(100)
Ceftriaxone	0(0.00)	0(0.00)	46(100)
Imipenem	5(10.86)	2(4.34)	39(84.78)
Tobramycin	2(4.34)	8(17.39)	37(80.43)
Amikacin	6(13.4)	4(8.69)	36(78.26)
Gentamycin	7(15.21)	8(17.39)	31(67.39)
Ciprofloxacin	0(0.00)	1(2.17)	45(97.82)
Tetracycline	2(4.34)	1(2.17)	97.82)
Colisitin	46(0.00)	0(0.00)	0(.00)

Table -3 Prevalence of Drug resistance among *S.aureus* isolates from VAP

Antibiotic	Susceptible	Intermediate	Resistant
Penicillin	0(0.00)	0(0.00)	31(100)
Oxacillin	2(6.45)	0(0.00)	29(93.54)
Vancomycin	31(100)	0(0.00)	0(0.00)
Ceftriaxone	2(6.45)	0(0.00)	29(93.54)
Azithromycin	1(3.25)	1(3.25)	29(93.54)
Tetracyclin	1(3.25)	0(0.00)	30(96.77)
Clidamycin	0(0.00)	1(3.25)	30(96.77)
Rifampin	6(19.35)	0(0.00)	25(80.64)
Ciprofloxacin	1(3.25)	1(3.25)	29(93.54)
Co-trimoxazole	6(19.35)	0(0.00)	25(80.64)
Erythromycin	2(6.45)	2(6.45)	0(0.00)
Gentamycin	3(9.67)	2(6.45)	28(90.32)
Chloramphenicol	29(93.54)	0(0.00)	0(0.00)

References:

- 1-Goel V, Hogade SA, Karadesai S. Ventilator associated pneumonia in a medical intensive care unit: Microbial aetiology, susceptibility patterns of isolated microorganisms and outcome. Indian J Anaesth. 2012; 56:558-62.
- 2-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 Respir Crit Care Med. 1998;15:21- 9.
- 3-Nair S, Sen N, Peter JV, Raj JP, Brahmadathan KN. Role of quantitative endotracheal aspirate and cultures as a surveillance and diagnostic tool for ventilator associated pneumonia: a pilot study. Indian Med Sci. 2008;62 :304-13.
- 4-Craven DE. Epidemiology of ventilator-associated pneumonia. Chest. 2000; 117:186S-187S.
- 5-Rea-Neto A, Youssef NC, Tuche F, Brunkhorst F, Ranieri VM, Reinhart K, Sakr Y. Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. Crit Care. 2008; 12:R56.
- 6-Ioannas M, Ferrer R, Angrill J, Ferrer M, Torres A. Microbial investigation in ventilator-associated pneumonia. Eur Respir J. 2001;17: 791-801.
- 7-Wiener-Kronish JP, Dorr HI. Ventilator-associated pneumonia: problems with diagnosis and therapy. Best Pract Res Clin Anaesthesiol. 2008; 22:437-49.
- 8-Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of

ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis.* 1991; 143:1121-9.

9-Wood AY, Davit AJ 2nd, Ciraulo DL, Arp NW, Richart CM, Maxwell RA, Barker DE. A prospective assessment of diagnostic efficacy of blind protective bronchial brushings compared to bronchoscope-assisted lavage, bronchoscope-directed brushings, and blind endotracheal aspirates in ventilator-associated pneumonia. *J Trauma.* 2003 55:825-34.

10-Rello J, Gallego M, Mariscal D, Soñora R, Valles J. The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 1997; 156:196-200.

11-Bassetti M, Taramasso L, Giacobbe DR, Pelosi P. Management of ventilator-associated pneumonia: epidemiology, diagnosis and antimicrobial therapy. *Expert Rev Anti Infect Ther.* 2012; 10:585-96.

12-Baselski V, Klutts JS. Point-Counterpoint: Quantitative cultures of bronchoscopically obtained specimens should be performed for optimal management in patients with ventilator associated pneumonia. *J Clin Microbiol.* 2013; 51:3740-744

13-CLSI

14- Porzecanski I, Bowton DL. Diagnosis and treatment of ventilator-associated pneumonia. *Chest.*2006; 130:597-604.

15- Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, Niederman MS, Rello J; EU-VAP Study Investigators. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors *ntensive Care Med.* 2013; 39: 672-681

16-Ariza J. Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude mortality. *Eur J Clin Microbiol Infect Dis.* 2013; 32:413-20

17- Depuydt PO, Vandijck DM, Bekaert MA, Decruyenaere JM, Blot SI, Vogelaers DP, Benoit DD. Determinants and impact of multidrug antibiotic resistance in pathogens causing ventilator-associated-pneumonia. *Crit Care. Crit Care.* 2008;12(6):R142.

18- Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med.* 2011 ; 15;184:1409-17.

19- Rello J, Ulldemolins M, Lisboa T, Koulenti D, Mañez R, Martin-Loeches I, De Waele JJ, Putensen C, Guven M, Deja M, Diaz E; EU-VAP/CAP Study Group. Determinants of prescription and choice of empirical therapy for hospital-acquired and ventilator-associated pneumonia. *Eur Respir J.* 2011 ;37:1332-9.

20- Japoni A, Vazin A, Davarpanah MA, Afkhami Ardakani M, Alborzi A, Japoni S, Rafaatpour N. Ventilator-associated pneumonia in Iranian intensive care units. *J Infect Dev Ctries.* 2011; 26:286-93.

- 21- Talaie H, Sabeti S, Mahdavinejad A, Barari B, Kamalbeik S. A survey of microorganisms and their sensitivity by E-test in ventilator-associated pneumonia at Toxicological-Intensive Care Unit of Loghman-Hakim Hospital. *Acta Biomed.* 2010; 81:210-6.
- 22- Afjeh SA, Sabzehei MK, Karimi A, Shiva F, Shamshiri AR. Surveillance of ventilator-associated pneumonia in a neonatal intensive care unit: characteristics, risk factors, and outcome. *Arch Iran Med.* 2012; 15:567-71.
- 23- Rahbar M, Hajia M. Detection and quantitation of the etiologic agents of ventilator-associated pneumonia in endotracheal tube aspirates from patients in Iran. *Infect Control Hosp Epidemiol.* 2006; 27(8):884-5.
- 24- Peña C, Gómez-Zorrilla S, Oriol I, Tubau F, Dominguez MA, Pujol M, Ariza J. Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude mortality *Eur J Clin Microbiol Infect Dis.* 2013 Mar;32 :413-20.
- 25- Vila J, Pachón J. Therapeutic options for *Acinetobacter baumannii* infections: an update. *Expert Opin Pharmacother.* 2012; 13; 2319-36.
- 26- Rello J, Molano D, Villabon M, Reina R, Rita, Quispe R, Previgliano I, Afonso E, Restrepo MI; Differences in hospital-and ventilator-associated pneumonia due to *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant) between Europe and Latin America: A comparison of the EUVAP and LATINVAP study cohorts *Med Intensiva.* 2012. <http://dx.doi.org/10.1016/j.medin.2012.04.008>