SPECTRUM OF VENTILATOR ASSOCIATED PNEUMONIA WITH EFFECT ON INTENSIVE CARE UNIT'S PATIENT OUTCOME

Wasib Ishtiaq, Abid Ilyas, Salman Assad*, Aayesha Qadeer, Haider Ghazanfar*, Tauqeer Sulehria*, Shoaib Saadat, Zain Ul Abideen, Aftab Akhtar

Shifa International Hospital Islamabad Pakistan, *Shifa College of Medicine Islamabad Pakistan

ABSTRACT

Objective: To evaluate the spectrum of ventilator-associated pneumonia (VAP) and relation of length of intensive care unit (ICU) stay, patient's age and gender on the likelihood of being discharged from the ICU.
Study Design: A cross sectional study.
Place and Duration of Study: Shifa International Hospital, Islamabad, Pakistan over a period of 12 months extending, from Apr 2015 to Apr 2016.
Material and Methods: We included 470 patients out of whom only 106 patients were diagnosed with VAP while on mechanical ventilation in ICU for >48 hours. A positive culture of tracheo-bronchial secretions, with any one of these; >48-h infiltrate on chest radiograph, fever of >38.3°C, leukocytosis of >12 × 10^9/ml and increase in tracheo-bronchial secretions established the diagnosis of VAP.
Results: The mean age of the male and female patients was 49.8 ± 18 years and 50.6 ± 21.4 years respectively with 16.6 ± 13 days as the mean duration of ICU stay. About 30.2% VAP patients had Acinetobacterbaumanni with 96.8% sensitivity to colistin, 27.4% patients had Klebsiella pneumonia with 72% and 62% sensitivity to colistin and carbapenems respectively and 15.1% patients had methicillin-resistant Staphylococcus aureus with 100% sensitivity to vancomycin. There was an increased incidence 60.4% of late-onset VAP compared to 39.6% early onset VAP. The overall mortality in VAP patients was 28.6%.
Conclusion: We recommend the empirical combination therapy of colistin, carbapenem, and vancomycin in VAP. No statistical significant association was found between length of ICU stay and patient's mortality. The odds of getting discharged were found to be 3.2 times greater for male participants as opposed to female patients. Decreasing age was associated with an increased likelihood of being discharged.

Keywords: Intensive care unit, Mortality, Ventilator associated pneumonia.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a significant concern for patients on mechanical ventilation in intensive care unit setting. Pneumonia affects 27 % of all critically ill patients and is the 2nd most common nosocomial infection among intensive care unit patients[1]. Ventilator-associated pneumonia (VAP) develops in critically ill patients after 48 hours of mechanical ventilation[2]. It ranges from 6 to 52% and can reach 76% in some specific settings[3]. Ventilator-associated pneumonia should be differentiated from hospital-acquired pneumonia which develops 48 hours after the admission to hospital and especially among patients who are not mechanically ventilated at the time of admission. The length of hospital stay is enhanced to seven to nine days by the presence of hospital-acquired pneumonia[4,5]. The risk of VAP is highest in the early course of mechanical ventilation and is estimated to be 3 percent per day during the first 5 days of ventilation, 2% per day during days 5-10 of ventilation and 1 percent per day after this[6].

The range of mortality due to ventilator-associated pneumonia (VAP) has been documented between 0 to 50%[7-11]. While determining mortality various results have been reported by many studies because of differences in suitable empirical medical therapy during the first 2 days and wide variation of documented

Correspondence: Dr Salman Assad, H-8/4 Shifa International Hospital Islamabad Pakistan *(Email: salmanassad91@gmail.com)*
Received: 09 Jun 2016; revised received: 24 Jun 2016; accepted: 27 Jun 2016

critically ill patients including acute respiratory distress syndrome (ARDS) patients, less-acute trauma patients and medical and surgical ICU patients. Organisms responsible for ventilator associated pneumonia affect the primary outcome in terms of mortality with higher mortality rates seen in VAP caused by P.aeruginosa, Acinetobacter baumanni and Stenotrophomonas maltophilia[12]. High clinical suspicion is required for diagnosing VAP along with radiographic examination, bedside assessment and microbiologic investigation of respiratory secretions. Aggressive analysis of factors leading to VAP and microbiological assessment is important in managing critically ill patients. Respiratory therapy interventions for prevention should be adopted. Our knowledge of VAP has developed significantly regarding pathogenesis, risk factors, diagnostic testing, therapies, and prevention by modifying risk factors. The spectrum of our study documents the most prevalent ventilator-associated pneumonia organisms and their sensitivities and resistance to various antibiotics. We also analyzed if there is any significant association or relation between the length of hospital stay and patient's outcome in terms of mortality.

MATERIAL AND METHODS

We carried out a cross-sectional study in Shifa International Hospital, Islamabad, Pakistan over a period of 12 months extending from April 2015 to April 2016 including 470 patients on mechanical ventilation in an intensive care unit (ICU) for more than 48 hours of a tertiary care centre. Consecutive non probability sampling was used to collect data. Using WHO sample size calculator, keeping 95% confidence level, absolute precision required 1%, sample size of 95 was calculated. Ventilator associated pneumonia was diagnosed in 106 patients only. Both male and female patients who were kept on a mechanical ventilator for >48 hours, having the age of greater than 15 years were included in the study. Those patients who were diagnosed with pneumonia at the time of admission or within 48 hours and patients of acute respiratory distress syndrome (ARDS) were excluded from our study. Date of starting mechanical ventilation, an indication of mechanical ventilation and form of patients' airway, i.e. orotracheal or tracheostomy, were recorded. In each patient, ventilator mode and settings were recorded and any change in setting was recorded daily. A positive culture of tracheobronchial secretions presenting with any one of these; >48-hours infiltrate on chest radiograph, fever of >38.3°C, leukocytosis of >12 × 10^9/ml and increase in tracheo-bronchial secretions established the diagnosis of ventilator-associated pneumonia. General physical examination, oxygen saturation and position of the patients were checked on a regular basis. Patients were effectively sedated during the preliminary stage of ventilation. Special investigations including the culture of blood, tracheal tube and urine, when required, were performed. Tip of the suction catheter was used to collect the sputum of the patients and then shifted to the laboratory using a sterile tube. VAP was diagnosed on clinical grounds based on the modified clinical pulmonary infection scoring system (CPIS) giving 0–2 points each for leukocyte count, fever, type of radiographic abnormality, oxygenation status, purulence and quantity and of tracheal secretions and result of gram stain and sputum culture (table-I). Culture and sensitivities of each organism to antibiotics as reported by the microbiology laboratory in Shifa International Hospital were recorded and analyzed. Empirical antibiotic therapy was started once the clinical suspicion of ventilator-associated pneumonia was established. Twelve hour arterial blood gases (ABGs) analysis of every patient was regularly done and suitable steps were taken to correct the abnormality. Binary logistic regression was performed to ascertain the effect of the length of ICU stay, patient's age and gender on the likelihood of patient being discharged from ICU with controlled infection and negative cultures. Patients which were still under treatment were not considered in logistic regression, *p*-value of less than 0.05 was considered as significant.

RESULTS

A total of 600 patients on mechanical ventilation in an intensive care unit (ICU) were approached out of which 470 patients agree to participate. Ventilator associated pneumonia was diagnosed in 106 patients only. The mean age of the patients was found to be 50.1 ± 19.3 years while the mean duration of ICU stay was found to be 16.67 ± 13.086 days. The mean age of the male patients was 49.86 ± 18.035 years while the mean age of the female patients was 50.60 ± 21.497 years. Out of the total 106 patients; 64/106 (60.4%) were male while 42/106 (39.6%) were females. Main symptoms of the patients diagnosed with VAP have been enumerated in table-II. About 76/106 (71.6%) of the patients had chest X-ray showing infiltrates. Out of the 106 participants who developed VAP; 42/106 (39.6%) of them developed it within the first 4 days after being placed on a ventilator while the remaining 64/106 (60.4%) developed it after the first 4 days.

Table-I: Clinical pulmonary infection scoring system[27].

CPIS* points	0	1	2
Tracheal secretions	Rare	Abundant	Purulent
Leukocyte count (mm3)	>4,000 and <11,000	<4,000 and >11,000	<4,000 or >11,000 + band forms
Temperature (°C)	>36.5 and <38.4	>38.5 and <38.9	> 39 or <36
PaO_2/FiO_2 ratio (mmHg)	<240 or ARDS**	-	≤ 240 and no ARDS
Chest radiograph	No infiltrate	Diffuse infiltrate	Localized infiltrate
Culture of tracheal aspirate	Negative	-	Positive

*Clinical pulmonary infection scoring system (CPIS), **Acute respiratory distress syndrome (ARDS).

Table-II: Common clinicopathologic features in patients with ventilator associated pneumonia.

Variables	Yes (N=106)
Fever	81 (76.4%)
Leukocytosis	82 (77.3%)
Purulent secretions	104 (98.1%)
Chest X ray Infiltrates	76 (71.6%)

Table-III: Distribution of bacterial isolates from patients diagnosed with ventilator associated pneumonia.

Organisms	Frequency and Percentage (%) (N=106)
Acinetobacter baumanni	32 (30.2%)
Klebsiella pneumoniae	29 (27.4%)
MRSA*	16 (15.1%)
Pseudomonas aeruginosa	10 (9.4%)
Escherichia coli	8 (7.5%)
Stenotrophomonas maltophilia	4 (3.8%)
Serratia marscescens	3 (2.8%)
Proteus	2 (1.9%)
Burkholderia cepacia	1 (0.9%)
VRE**	1 (0.9%)

*Methicillin resistant Staphylococcus aureus (MRSA), **Vancomycin resistant enterococci (VRE).

30.2% VAP patients had Acinetobacter baumanni with 96.8% sensitivity to colistin, 27.4% patients had *Klebsiella pneumoniae* with 72% and 62% sensitivity to colistin and carbapenems respectively and 15.1% patients had methicillin-resistant *Staphylococcus aureus* with 100% sensitivity to vancomycin and linezolid (table-IV). There was an increased incidence 60.4% of late-onset VAP compared to 39.6% early onset

VAP. The overall mortality in our study was 28.6% (table-III). We found multi-drug resistance (MDR) in Klebsiella pneumonia and E-coli, extensively drug resistance (XDR) in Acinetobacter baumanni with only sensitivity to colistin and pan-drug resistance (PDR) in one patient only diagnosed with Acinetobacter baumanni (table-IV). 60/106 (71.4%) patients were discharged while 24/106 (28.6%) died of illness. The remaining 22/106 (20.8%) participants of the study are still undergoing treatment. Binary logistic regression was performed to ascertain the effect of length of ICU stay, patient's age, gender on the likelihood that the participant will be discharged from the ICU with controlled infection and negative cultures. The model explained 16.8% of the variance in patient's outcome and correctly classified 73.8% of cases (Nagelkerke R2). In our study no statistical association was found between length of ICU stay and patient's mortality (*p*-value ≥0.05). The odds of getting discharged were found to be 3.2 times greater for male patients as opposed to female patients. This was found to be statistically significant (*p*-value=0.02). Decreasing age was associated with an increased likelihood of being discharged (*p*-value=0.04).

DISCUSSION

Ventilator-associated pneumonia (VAP) is one of the most documented hospital-acquired infections among mechanically ventilated patients and is associated with increased mortality, ICU stay, and health-related costs. VAP occurrence is related to placement of endotracheal tube and is closely related to intubation as well. Hence, effective preventive measures can be taken in ventilated patients to prevent the ventilator associated pneumonia[12]. We document the incidence of VAP cases to be 106/470 (22.5%) compared to VAP incidence ranges reported between near 0 to 25%, with higher risk during the first few days of mechanical ventilation[13]. There is an increased incidence of 64/106 (60.4%) patients with late onset VAP after the first 4 days of mechanical ventilation compared to early-onset VAP developed in 42/106 (39.6%) patients within the first 4 days after being placed on the ventilator. Similar results presented by a study conducted by Golia et al. with 44.23% patients had early-onset (<4 days mechanical ventilation) VAP and 55.77% had late-onset (>4 days mechanical ventilation) VAP[14]. The overall mortality in our

Table-IV: VAP associated organisms and their sensitivity to antibiotics.

Antibiotics	Acinetobacter baumanni N=32	Klebisella pneumonia N=29	MRSA* N=16	Pseudomonas aeroginosa N=10	E-coli** N=8	Stentotrophomonas N=4	Proteus N=2
Amikacin	1 (3%)	17 (58.6%)	-	6 (60%)	8 (100%)	0	2 (100%)
Ceftazidime	0	0	-	5 (50%)	0	1 (25%)	1 (50%)
Ciprofloxacin	0	8 (27%)	-	3 (30%)	1(12.5%)	3 (75%)	2 (100%)
Imipenem	0	18 (62%)	-	3 (30%)	7 (87.5%)	0	2 (100%)
Piperacillin	0	14 (48.2%)	-	4 (40%)	5 (62.5%)	2 (50%)	2 (100%)
Meropenem	0	18 (62%)	-	2 (20%)	7 (87.5%)	0	2 (100%)
Levofloxacin	0	2 (6%)	-	0	0	0	0
Ceftriaxone	1 (3%)	1 (3%)	-	0	0	0	0
Cefoperazone /Sulbactum	2 (6%)	14 (48.2%)	-	3 (30%)	5 (62.5%)	2 (50%)	2 (100%)
Colistin	31 (96.8%)	21(72.4%)	-	8 (80%)	3 (37.5%)	0	0
SeptranDS	5 (15.6%)	5 (17.2%)	11 (68.7%)	0	1 (12.5%)	3 (75%)	1 (50%)
Linezolid	-	-	16 (100%)	-	-	-	-
Vancomycin	-	-	16 (100%)	-	-	-	-

*Methicillin resistant staphylococcus aureus (MRSA), **Escherichia coli.

study was 28.6% compared to 44% documented by Kumar et al[15]. Gadani et al. reported the order of incidence of organism Pseudomonas (43.2%), Klebsiella (18.91%), followed by Methicillin-resistant Staphylococcus aureus (MRSA), E. coli, Acinetobacter, and Streptococcus pneumonia[16]. While we documented bacterial isolates as Acinetobacter 30.2%, Klebsiella 27.4% and MRSA 15.1%, Pseudomonas 9.1 % and E-coli 7.5%.

Multidrug resistance (MDR) is an acquired resistance to at least one agent in 3 or more antimicrobial groups, extensive drug resistance (XDR) is a resistance to at least 1 drug in all but 2 or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only 1 or 2 groups) and pan-drug resistance (PDR) is a resistance to all agents in all antimicrobial categories[17]. We found multi-drug resistance (MDR) in Klebsiella pneumonia and E-coli, extensive drug resistance (XDR) in Acinetobacter with only sensitivity to colistin and pan-drug resistance (PDR) in one patient only diagnosed with Acinetobacter (table-IV). Although organisms responsible for VAP can disseminate to the blood or pleural space in less than 10 percent cases, if an organism known to cause ventilator associated pneumonia is cultured with clinically suspected pneumonia, targeted therapy should be started. Therefore, evaluation of suspected VAP should include two sets of blood cultures and a thoracocentesis for non-loculated pleural effusions of ≥10 mm in diameter on a lateral decubitus chest X- ray[18]. Ultrasound guidance may be required in case of loculated effusion. The sensitivity of blood cultures is less than 25 percent for ventilator associated pneumonia diagnosis but once cultures are positive, there are 64 percent cases where organisms may come from extrapulmonary site of infection[19,20]. We did not include blood cultures as diagnostic criteria for VAP because of lower sensitivity. Excess mortality has been reported with delays in the administration of appropriate antibiotic management for ventilator associated pneumonia[21]. Iregui et al. described 69.7% mortality due to a delay of 24 hour or more in starting an appropriate therapy, compared to 28.4% in VAP patients treated without the delay (p<0.001)[22]. These results were comparable to 28.6% mortality documented in our setting where appropriate antibiotic started without delays. Consequently, once VAP is considered, cultures must be obtained quickly and treatment initiated without delay. In our study, 30.2% VAP patients had Acinetobacter with 96.8% sensitivity to colistin, 27.4% patients had Klebsiella with 72% and 62% sensitivity to colistin and carbapenems respectively and 15.1% patients had methicillin-resistant Staphylococcus aureus with 100% sensitivity to vancomycin and linezolid. We recommend the empirical use of colistin with carbapenems and vancomycin in ventilator-associated pneumonia. Renal function tests should be monitored with combination therapy of vancomycin and colistin as this combination significantly increases the risk of renal failure[23]. Durante-Mangoni et al. concluded rifampicin should not be routinely combined with colistin in extensively drug resistance (XDR) A. baumannii infections because of non-reduction of 30 day mortality by the addition of rifampicin to colistin[24]. Directed therapy against multidrug resistant carbapenemase - producing K. pneumonia, extensive drug-resistant A. baumannii or P. aeruginosa) should be done in intensive care unit[25]. Caceres et al. documented that female gender was not linked with clinically worse outcomes or increased utilization of resources compared to the male gender in intensive care unit diagnosed pneumonia[26]. Odd of getting discharged was found to be 3.2 times greater for male participants as opposed to female participants diagnosed with ventilator-associated pneumonia (VAP) (p-value=0.02). Decreasing age was associated with an increased likelihood of being discharged (p-value=0.04).

CONCLUSION

Although the exact incidence and impact of VAP are still debatable, it still presents an important challenge for healthcare professionals. We recommend empirical use of combination therapy with colistin, carbapenems and vancomycin in ventilator associated pneumonia

with renal function tests monitoring because of three most common reported infections in our setting (i.e. 30.2% patients of Acinetobacter baumanni with 96.8% sensitivity to colistin, 27.4% patients of Klebsiella pneumoniae with 72% and 62% sensitivity to colistin and carbapenems respectively and 15.1% patients had methicillin-resistant Staphylococcus aureus with 100% sensitivity to vancomycin). Preventive strategies focus on better secretion management and on reduction in bacterial colonization. No statistical association was found between length of ICU stay and patient's mortality. The odd of getting discharged was found to be 3.2 times greater for male participants as opposed to female participants. This was found to be statistically significant (*p*-value=0.02). Decreasing age was associated with an increased likelihood of being discharged (*p*-vlaue=0.04).

ACKNOWLEDGEMENT

All authors of this research article pay special thanks to Shifa International Hospital Islamabad Pakistan and Mrs. Ruth Samuel (Nurse) and Mr. Khawar Yaqoob (BSN) for their contribution.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Gaynes Nosocomial infections in medical intensive care units in the United States. Crit Care Med 1999; 27: 887-92.
2. Davis KA. Ventilator- associated pneumonia: a review. J Intensive Care Med 2006; 21: 211–26.
3. Koenig SM, Truwit JD. Ventilator- associated pneumonia: diagnosis, treatment, and prevention. Clin Microbiol Rev 2006; 19: 637–57.
4. Chastre J, Fagon JY. Ventilator- associated pneumonia. Am J Respir Crit Care Med 2002; 165: 867–903.
5. Rello J, Ollendorf DA, Oster G, Montserrat V, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator- associated pneumonia in a large US database. Chest 2002; 122: 2115-21.
6. 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: 440-43.
7. Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. Am J Respir Crit Care Med 1996; 153: 343-49.
8. Craig CP, Connelly S. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am J Infect Control 1984; 12: 233-38.
9. Cunnion KM, Weber DJ, Broadhead WE, Hanson LC, Pieper CF, Rutala WA. Risk factors for nosocomial pneumonia: comparing adult critical-care populations. Am J Respir Crit Care Med 1996; 153: 158-62.
10. Kappstein I, Schulgen G, Beyer U, Geiger K, Schumacher M, Daschner FD. Prolongation of hospital stay and extra costs due to ventilator- associated pneumonia in an intensive care unit. Eur J Clin Microbiol Infect Dis 1992; 11: 504-08.
11. 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.
12. Kollef MH, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator- associated pneumonia in determining patient mortality. Chest 1995; 108: 1655-62.
13. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital- acquired, ventilator- associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171(4): 388-416.
14. Chastre J, Fagon JY. Ventilator- associated pneumonia. Am J RespirCrit Care Med 2002; 165(7): 867-903.
15. Golia S, Sangeetha KT, Vasudha CL. Microbial profile of early and late onset ventilator associated pneumonia in the intensive care unit of a tertiary care hospital in bangalore, india. J Clin Diagn Res 2013; 7(11): 2462–2466.
16. Mallick Uk, Faruq MO, Ahsan A, Fatema K, Ahmed F, Zaman MA, et al. Spectrum of early onset and late onset ventilator associated pneumonia (vap) in a tertiary care hospital of bangladesh: A prospective cohort study. Bangladesh Crit Care J 2015; 3(1): 9-13.
17. Gadani H, Vyas A, Kar AK. A study of ventilator-associated pneumonia: Incidence, outcome, risk factors and measures to be taken for prevention. Indian J Anaesth 2010; 54(6): 535–540.
18. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18(3): 268-81.
19. Chastre J, Fagon JY. Ventilator- associated pneumonia. Am J Respir Crit Care Med 2002; 165: 867-903.
20. Bryan CS. Nosocomial pneumonia: Blood cultures remain useful. Chest 1999; 116: 859-60.
21. Luna CM, Videla A, Mattera J, Vay C, Famiglietti A. Niederman. Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. Chest 1999; 116: 1075-84.
22. Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, et al. Jolly. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997; 111: 676-85.
23. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002; 122: 262-68.
24. Garnacho-Montero J, Amaya-Villar R, Gutiérrez-Pizarraya A, Espejo-Gutiérrez de Tena E, Artero-González ML, Corcia-Palomo Y, et al. Clinical efficacy and safety of the combination of colistin plus vancomycin for the treatment of severe infections caused by carbapenem-resistant Acineto-bacterbaumannii. Chemotherapy 2013; 59(3): 225-31.
25. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: A multicenter, randomized clinical trial. Clin Infect Dis 2013; 57(3): 349-58.
26. Garnacho-Montero J, Corcia-Palomo Y, Amaya-Villar R, Martin-Villen L. How to treat VAP due to MDR pathogens in ICU patients. BMC Infect Dis 2014; 14: 135.