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VENTILATOR-ASSOCIATED PNEUMONIA;

MICROBIOLOGY, MULTIDRUG RESISTANCE IMPACT AND ASSOCIATED RISK FACTORS IN TERTIARY HOSPITALS SETTINGS

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ABSTRACT… Background: Patients associated with VAP having mortality rates range from 20 to 50% and this may extend up to 70% when multi-resistant and invasive pathogens accountable for infection, however, VAP is also interrelated with noteworthy rate of morbidity, extended period of stay in ICU, protracted MV, and augmented hospitalization cost. **Objectives:** To review the risk factors, incidence and transience rate of mortality for ventilator-associated pneumonia. **Design:** Prospective and cross sectional way. **Period:** From April 2016 to December 2016. **Setting:** Different Tertiary Care Institutes of Karachi, Pakistan. **Method:** A structured data collection form was prepared to record the information and validated using spearman correlation coefficient and Cronbach's α value. Value of $\alpha = 0.902$ and $p = 0.913$ have revealed the suitable degree of reliability and uniformity. Data was collected with respect to gender, age, antibiotic utilization record, and main diagnosis outcomes. Microbiological basis of ventilator-associated pneumonia was assessed using patient lab record for rate and seclusion of organism. **Results:** In this study a detail of significant virulence factor articulated by these microorganisms has been depicted. Statistically insignificant differences were observed among the groups with respect to clinical and demographic characteristics like mean age, gender, infection severity scores (SOFA, MODS, CPIS and APACHE II), immune status of patients and type of the cases including surgical or clinical scenario. 39.3% patients developed early onset while 60.6% of cohort was observed with late onset of VAP. **Conclusion:** The precise microbial source of VAP are numerous and diverse. The realistic challenge at the present time is to portray the authentic approximate of the clinical consequences associated with VAP. Henceforth such investigations may be supportive in origination of the most favorable institutional antimicrobial strategy to reduce the associated complications of this threat.

Key words: Multi Drug Resistance (MDR), Risk Factors, Ventilator Associated Pneumonia.

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INTRODUCTION

Ventilator associated pneumonia (VAP) is the most common hospital acquired infection, encountered patients in intensive care unit and usually develops after 48 hours of endotracheal intubation and mechanical ventilation.[1-2] 1-3% increment in risk of VAP has been reported in literature on mechanical ventilation (MV). The majority cases of VAP are emerges due to bacterial pathogens that usually colonize the area of oropharynx and gut. They may be acquired via communication by hospital staff or from environmental surfaces.[3-4]

VAP is as a matter of course classified as either "early onset" if it is developed within 4–7 days following intubation, or "late-onset" VAP if it is developed after 4–7 days of ventilation. Pathogens accountable for Early-onset VAP include Haemophilus species, streptococci including S. pneumoniae, methicillin sensitive S. aureus, and susceptible strains of Enterobacteriaceae. In addition, these pathogens may also develop

late-onset VAP, but multiple-drug-resistant microbes' i.e Acinetobacter, Pseudomonas, Stenotrophomonas species, and MRSA are more common in the late-onset VAP period and typically exhibit high levels of antibiotic resistance. These pathogens, and enteric Gram-negative bacilli producing extended-spectrum beta lactamases, have been termed "potentially drug-resistant" pathogens.[5]

More than a few criteria have been projected for identifying VAP in clinical situations that may include clinical manifestation of conditions, techniques to attain and infer broncho-alveolar samples, radiographic examinations, and application of host response biomarkers. Owing to the lack of a suitable gold standard customary to specific scenario, the exactness/ meticulousness of such methods in diagnosing VAP is contentious.[6] The Infectious Diseases Society of America (IDSA) and The American Thoracic Society (ATS) guidelines recommend obtaining lower respiratory tract samples for culture and microbiology and these samples can be analyzed qualitatively (with a threshold count of the bacterial growth to differentiate between colonization and infection of the lower airways) or quantitatively (absence or presence of pathogenic microbes in the culture). This guideline also permits use of tracheal aspirates for their negative predictive value (94 % for VAP).[7-8]

There are limited data regarding the usefulness of quantitative in contrast to qualitative cultures. A few studies illustrated that quantitative cultures should be used in order to evade false-positive results, but little is known about the specificity and sensitivity of quantitative culture findings in critically ill patients who have formerly received extended -spectrum antibiotics.[9-10] However, culture results for bronchial or tracheal samples may be available delayed in the course of an episode of VAP and should not be used to decide whether to treat, especially in critically ill patients.[11] In contrast, culture results/test should be used to adjust (narrow or broad antibiotic spectrum) or withdraw empirical antibiotic treatment–which shown to be valuable, with no increase in mortality, and that directs hospital staff to seek other unsuspected pivot of infection.[6] Delayed diagnosis and inadequate delay in the commencement of treatment may be linked with detrimental effects in patients with VAP, conversely; a wrong diagnosis may escort to ensuing complications and needless treatment allied with therapeutic failure. Early, appropriate diagnosis is, therefore, essential in the management of VAP patients.[12] This study is aimed to evaluate the clinical consequences of VAP with following objectives;

- To calculate the incidence and observed risk factors associated with VAP.
- To evaluate the type and frequency of isolates and related antibiotic utilization pattern.
- To utilize the predictors and associated factors for diagnosis and severity of VAP (CPIS and APACHE II, SOFA and MOD Scores)

MATERIAL AND METHOD

Study Design

This study was carried out in prospective and cross sectional manner in tertiary care settings/ hospitals, Karachi. Study was designed to determine the associated risk factors for VAP pathogens involved and applicable investigative protocols for ventilator-associated pneumonia in order of incidence.

Procedure of Data Collection

Data was collected during the period of April, 2016 to December, 2016. Medical records were assessed in order to acquire the related information. A structured data collection form was prepared to record the information and validated using spearman correlation coefficient and Cronbach's α value. Value of $\alpha = 0.902$ and $p = 0.913$ have revealed the suitable degree of reliability and uniformity.

Ethical Contemplation

The presented project was approved from Institutional ethical committee proceeding to study (0251115SZPHARM). The secrecy of patient's records was sustained meticulously during the study period. Hospitals approvals were also obtained prior to study.

Inclusion Criteria
Patients were included who were ventilated either with or without VAP based on radiological and clinical evidences. The judgment of VAP was ingrained on the basis of the agreement among physicians using clinical or radiological details.

Exclusion Criteria
Patients admitted with COPD and pneumonia in ICU.

Sample Size
The total of 150 cases was incorporated in this study that was mechanically ventilated. A total of 33 VAP cases were observed. The value of prevalence[13-15] was taken 27%.

Study Protocol
During the study period, VAP has been confirmed by well trained intensivists and a pulmonologist. Evaluation of all ventilated patients was carried out during the study period from selected hospitals. A routine surveillance of cultures of tracheal aspirates for multidrug-resistant (MDR) pathogens was also performed from medical records. Data was collected with respect to gender, age, antibiotic utilization record, and main diagnosis outcomes. Microbiological basis of ventilator-associated pneumonia was assessed using patient lab record for rate and seclusion of organism. Furthermore bio-chemical and haematological screening results, chest x-rays and microbial samples of blood, nasopharynx, and tracheal aspirates reports were consulted for clinical outcomes. If there should be an occurrence of any question amid the gathering and investigation of any data, particular division/ doctor was consulted. Even though more than a few multiple organ dysfunction scoring methods[16] have been portrayed in literature, the Sequential Organ Failure Assessment (SOFA) score[17] and the Multiple Organ Dysfunction (MOD) score[18] are mainly functional. These scores were calculated using online calculators. For computation of Clinical pulmonary infection score (CPIS)[19] following diagnostic criteria was taken into consideration of VAP.

Diagnosis of Ventilator-Associated Pneumonia
Diagnostic criteria which was observed during the study based on the following parameters when any patient on mechanical ventilation for at least 48 hours have shown a new or continuing pulmonary infiltrate on the chest radiograph in connection with any of the subsequent features:

- dullness or rales to percussion lying on chest inspection;
- new commencement of purulent sputum or alter in sputum quality; reduction of 10% in any case in arterial oxygen tension or fractional (inspired) oxygen ratio;
- excess of leucocytes (12,000/mm3) or less than 4000/mm^3;
- positive cultures (blood or pleural);
- axial temperature more than 37.8°C or less than 36.0°C in case of no antipyretic treatment.

Statistical Analysis
The descriptive data was statistically investigated using SPSS Version 20. Results were inferred through frequencies and percentages.

RESULTS
A prospective evaluation of a total of 150 patients was carried out and amongst them 33 patients was found with VAP. The mean age was found to be 65.49 ± 13.45 and 61.22 ± 18.23 years respectively in MDR and drug sensitive groups. A sum of 20 patients (60.6%) were male and 13 (39.3%) were female in VAP group. The mean APCHE II score was 18 ± 6.3 and 22 ± 4.8 for sensitive and MDR cohort. Clinical patient were in majority in contrast to surgical patients (Table-II). While Table-I demonstrates the associated risk factors for VAP pathogens. Figure-1 depicts the comparative magnitude of frequent microorganisms of ventilator-associated pneumonia (N=32). Moreover Table-III presents the diagnostic and investigative protocols for ventilator-associated pneumonia in order of incidence. Figure-2 describes the antibiotic details prescribe in VAP and Figure-3 illustrates the association among the sensitivity of the microbial pathogens causing VAP and hospital mortality.

Clinical Isolates of Microbial Species	Associated Risk Factors
Methicillin-sensitive Staphylococcus aureus (MSSA) Streptococcus pneumoniae Methicillin resistant Staphylococcus aureus (MRSA) Haemophilus influenzae Pseudomonas aeruginosa Acinetobacter species	☐ Absence of antibiotic therapy ☐ Smoking ☐ Chronic obstructive pulmonary disease, acute respiratory distress syndrome. ☐ bronchoscopy ☐ Steroid therapy ☐ Longer duration of mechanical ☐ ventilation ☐ Duration of current hospitalization 5 days or longer ☐ Prior antibiotic therapy ☐ High frequency of antibiotic resistance ☐ Chronic dialysis (within 30 days) ☐ Head trauma ☐ Neurosurgery ☐ Gross aspiration ☐ Immunosuppressive disease or therapy

Table-I. Associated risk factors for VAP pathogens[20-22]

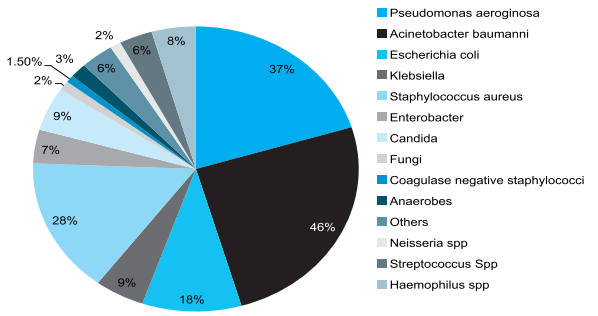

Figure-1. Comparative Magnitude of Frequent Origins of Ventilator-Associated Pneumonia (n=32)

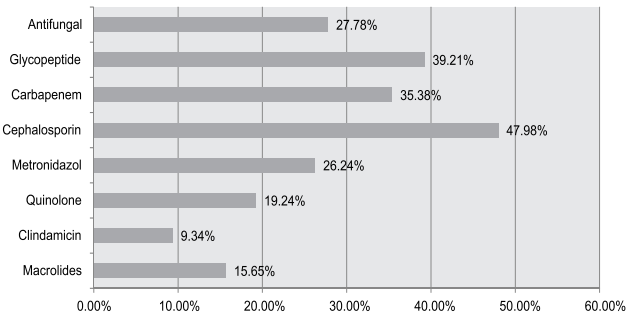

Figure-2. Prescribing detail of antimicrobials agents in VAP

Characteristics		Patients Without VAP N (%)	Patients With VAP N (%)	P-value
Frequency		117 (78.0%)	33 (22.0%)	0.05
Major Attribute of Patients With VAP (N=33)				
Attributes		**Drug-sensitive Microorganism (N=11)**	**MDR Microorganism (N=22)**	**P-value**
Age (years)		65.49 ± 13.45	61.22 ± 18.23	0.19
Sex	Female	4 (36.36%)	9 (28.12%)	0.81
	Male	7 (63.63%)	13 (43.75%)	
Immunological status	Immuno-competent	6 (54.54%)	12 (54.54%)	0.52
	Immuno-compromized	5 (45.45%)	10 (45.45%)	
Time of VAP onset	Early	7 (63.63%)	6 (27.27%)	0.74
	Late	4 (36.36%)	16 (72.72%)	
Patient Type	Clinical	9 (81.81%)	17 (77.27%)	0.45
	Surgical	2 (18.18%)	5 (22.72%)	
Drug treatment prior to VAP	Prior use of antibiotics within 30 days	10 (90.90%)	19 (86.36%)	0.34
	No utilization of antibiotics	1 (9.09 %)	3 (13.63%)	
Time of mechanical ventilation (days)		14.3 ± 20.5	23.7 ± 221.6	0.85
ICU stay (days)		28.9 ± 24.7	31.2 ± 19.3	0.59
APACHE II Score		18 ± 6.3	22 ± 4.8	0.23
SOFA score		7 ± 3.7	9 ± 3.0	0.46
MOD score		3.1± 2.3	3.9 ± 2.5	0.42
CPIS		8 ± 1.4	8 ± 1.7	0.65

Table-II. Base line characteristics of patients with VAP

Note: Acute physiology and chronic health evaluation II (APACHE II) criteria: multiple organ dysfunction score (MODS); Sequential Organ Failure Assessment (SOFA)

Diagnostic criteria	N=33 (Frequency %)
Fever	21 (63.63%)
Minimum 10% decline in the ratio of PaO_2/FiO_2	13 (39.39%)
Leukocytosis	23 (72.72%)
Purulent tracheal secretion	25 (75.75%)
Leucopenia	2 (6.06%)
Hypothermia	2 (6.06%)
dullness to percussion or Rales on chest assessment	7 (21.21%)
Blood positive cultures	5 (15.15%)

Table-III. Investigative protocols for ventilator-associated pneumonia in order of incidence
Note: PaO_2: arterial oxygen tension / FiO_2: fractional inspired oxygen

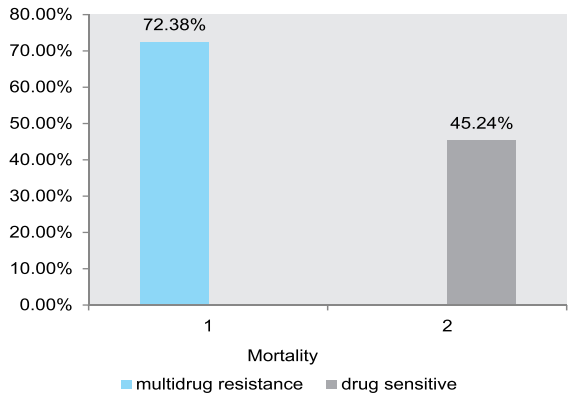

Figure-3. Association among the sensitivity of the microbial pathogens causing VAP and hospital mortality

DISCUSSION

Ventilator-associated pneumonia (VAP) is a widespread problem of MV support for patients with discriminating respiratory failure and is connected with amplified co-morbidity, higher transience rate and augmented costs of treatment. Knowledge of the VAP microbiology is vital for initiation of most favorable antibiotic remedy for beneficial outcomes.[20] Frequent pathogens consist of Gram-negative bacilli, Pseudomonas, Enterobacteriaceae, Streptococci, Staphylococci and Haemophilus species. VAP is mainly diagnosed by microbiological, clinical, and radiographic basis.[21]

Definite VAP pathogens occur in frequent way so distinctive situations of infectivity and relation of risk factors for such conditions can be described in agreeable manner. The inimitable microbiological characters of such organisms are dissimilar from others.[22-24] In this study a detail of significant virulence factor articulated by these microorganisms has been depicted in Table-I.

Out of 150 total patients only 33 patients developed VAP. This cohort was classified in two groups: individuals developed VAP by MDR bacteria (22 cases; 66.66%) and others caused by drug-sensitive isolates (11cases; 33.33%). Statistically insignificant differences were observed among the groups with respect to clinical and demographic characteristics like mean age, gender, infection severity scores (SOFA, MODS, CPIS and APACHE II), immune status of patients and type of the cases including surgical or clinical scenario (Table-II). A total of 13 patients (39.3%) developed VAP in first 5 days during ventilation and disclosed as early-onset of VAP, while 20 (60.6%) developed VAP after the 5th day and considered as late onset of VAP. In early-onset cohort, MDR pathogens were accountable for 6 (27.2%), in contrast with 16 (72.72%) of the cases of late-onset (Table-II). Concerning immune status, 18 individuals (54.5%) were considered immune-competent and the rest was immune-compromised. MDR microorganisms were liable for 12 (54.54%) in the earliest and10 (45.45%) in later cluster. Out of these 26 (78.7%) followed clinical treatment category while rest were surgical procedure group. Multidrug-resistant microorganisms caused 17 (77.27%) of the VAP cases in the clinical group and 5 (22.72%) of surgical cases. Judgment against VAP caused by MDR species with VAP emerges due to drug-sensitive microbes mechanical ventilation time (23.7 ± 21.6 days vs. 14.3 ± 20.5 days), length of ICU stay (31.2 ± 19.3 days vs. 28.9 ± 24.7 days) (Table-II). In another study author determined the various clinical and epidemiological factors related to MDR microbes and drug sensitive organism in the development of VAP.[29]

Various clinical forecasting rules like the SOFA and APACHE II scores are supposed to considered on all patients residing in the ICU with the intention of find out the intensity of acuity and risk of mortality. Application of this information is widespread such as to provide a prognosis detail to caregivers, intended for clinical trials, or as quality assessment tool. The SOFA score is not premeditated to manipulate medical supervision.[25] Per se, it ought not to be used with dynamism or to decide the interventional success or failure in the ICU. An initial SOFA score <9 predicted a mortality < 33% while score of 9-11 predicted a mortality 40-50%. A mortality of 95% is predicted with SOFA score >11. in addition, the presentation of these scores may be pretentious by the treatment used to continue the specific protocol.[26]

The explicit bacterial grounds of VAP are illustrated in Figure-1. The most widespread pathogen was Acinetobacter baumanni comprised of 24% of bacterial isolates. subsequently second common specie was P. aeruginosa (37%). Other than these S. aureus isolates (28%), Escherichia coli (18%) and Klebsiella species were 9%. Enterobacter species and candiad were found to be 7% and 9% respectively. While rest of the least frequent organisms like coagulase-negative staphylococci, Haemophilus species, Neisseria, streptococci, fungi and other isolates were portrayed in Figure-1. Other researchers also investigated the bacterial pathogens responsible for VAP. Various studies on sensitive and multi drug resistant isolates were carried out over the couple of years.[8-9,27] In one of the study the highest proportion of Pseudomonas aeruginosa isolates were calculated as MDR organism for VAP.[28]

Rate of mortality in this study in both groups was found to be 72.38% and 45.24% in MDR and drug sensitive cohort respectively. Statistics in the VAP literature reveals that MDR bacteria is connected with elevated rate of mortality. Chastre and Fagon[30] confirmed, by uniting numerous researches that preliminary empirical management looks to demonstrate an imperative role in the projection of such conditions with better prognosis. Mortality associated to pseudomonas is particularly high, frequently higher than 70% - 80%. Kollef et al.,[31] further confirmed these findings of higher mortalities associated with P. aeruginosa and Acinetobacter spp.

In the VAP group fever was present in 21 (63.3%) evaluations, while rate of leucocytosis and purulent secretion was found to be 72.72% and 75.75% respectively. Leucopenia, Hypothermia with similar proportion and percussion on chest assessment were observed by the therapist in 2 (6.06%) and 7 (21.21%) evaluations. Results of blood positive culture and decrease in PaO_2/FiO_2 ratio were summarized in Table-III.

On the whole, 86.5.8% of patients were receiving as a minimum one antibiotic. The most repeatedly administered group of antibiotics was cephalosporin's (47.9%), glycopeptides (39.2%), carbapenem (35.3%), and antifungal (27.7%). Detail of rest of antibiotic utilization frequencies is presented in Figure-2. Other investigators emphasized the significance of early institution of antibiotics treatment in VAP. Moreover, it has been elucidated from literature that clinical and radiological examinations may be taken as vital options over the other methods like %age of leucocytes or bronchial specimens as an avenue for fast confirmation.[32-33]

CONCLUSION

VAP is the major threat for ICU patients receives mechanical ventilation. The magnitude of complexicities and mortalities are significantly higher in clinical scenario than in surgical patients. While frequency may vary in accordance to the case bases and etiology of the agent involved. Over the past years only a diminutive number of investigations were carried out in Pakistan to evaluate the role of various quantitative methods in the appropriate diagnosis of VAP. It is further concluded that MDR bacterial infections are associated with higher mortalities.

Henceforth suitable empirical management with antibiotics is considered important prognostic measure. But still many challenges in adaptation of such systems are worthy like increasingly bacteria resistance. Henceforth systems with better specificity and enhanced sensitivity are

recommended.

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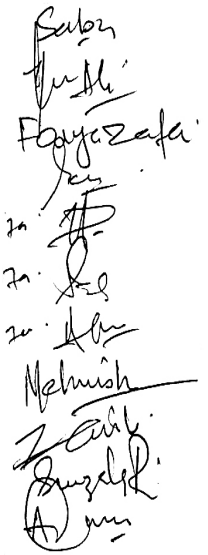
1	Saba Zubair	Equal contribution by all	
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