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ORIGINAL ARTICLE

Is the classification of Ventilator-Associated Pneumonia as early and late-onset useful? A comparison of Microbial Profile, Antibiotic Susceptibility and Mortality

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ABSTRACT

Aim: To see the microbial profile of early and late-onset ventilator-associated pneumonia, antibiotic susceptibility and mortality rate.

Methods: Retrospective cross-sectional study in 18-month period from 1st January 2023 to 31st June 2024 in Surgical ICU of Doctors Hospital and Medical Centre, Lahore, Pakistan. Data was analyzed using the IBM SPSS 29.0 software, and an Excel sheet was used to make a table of isolates and their sensitivity to antibiotics. Descriptive statistics like standard deviation and mean are used. One sample t-test was applied. SPSS and Excel sheet files are provided with the text. The P-value was set at <0.05, and a confidence interval of 95% is taken.

Results: A total of 46 ventilator associated pneumonia (VAP) were recorded during our study period of 18 months. Out of 46 cases, 13 (28.2%) were early-onset VAP and 33 (71.7%) were late-onset VAP. Males being more admitted in our surgical ICU, their number of VAP is also high, that is, 31(67.3%), while females constitute 15 (32.6%) cases. Among the early-onset VAP, the most common isolates were Pseudomonas aeruginosa 4(30.7%), Candida albicans 4(30.7%), Klebsiella pneumonia 2(15.38%), followed by each one of the Acinetobacter, Burkholderia, and E. coli. While in the late-onset VAP, isolates that appeared on tracheal cultures were Acinetobacter 8(24.2%), Klebsiella 8(24.2%), Pseudomonas 7(21.2%), Staphyloccus aureus 3(9.09%), Burkholderia 2(6.06%), Candida 2(6.02%), Proteus mirabilis 1(3.03%), E. coli 1(3.03%) and Enterobacter cloacae 1(3.03%). Almost all gram-negative organisms were sensitive to colistin except one E. coli. All Pseudomonas and Acinetobacter isolates were resistant to carbapenems (100% resistance), while Klebsiella is only 40% (4 out of 10) sensitive to carbapenems, E. coli 50% (1 out of 2), Burkholderia 66.6% (2 out of 3) and Proteus mirabilis was 100% sensitive. Klebsiella is 70% sensitive to chloramphenicol. Minocycline has 100% susceptibility for Acinetobacter, Enterobacter, and Staphylococcus aureus, while it has 60% susceptibility to Klebsiella and 33.3% for Burkholderia.

Conclusion: At the end of this study period of 18 months, we conclude that VAP is mainly caused by MDR bacteria, especially Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter Baumanni, in our settings, irrespective of the duration of onset. We suggest that broad spectrum MDR cover, including colistin, along with gram positive cover like vancomycin, linezolid, or teicoplanin, should be started as an empirical therapy to prevent the onset of early or late VAP.

Keywords: Ventilator associated pneumonia (VAP), Intensive Care Unit (ICU), Mechanical ventilation, Early Onset VAP, Late Onset VAP, Antimicrobial resistance

INTRODUCTION

Ventilator-Associated Pneumonia (VAP) is a significant healthcare concern, particularly in intensive care units (ICUs), where patients require prolonged mechanical ventilation. The incidence of VAP varies widely, affecting approximately 10% to 25% of patients who are ventilated for more than 48 hours[1].

This condition is not only prevalent but also associated with substantial clinical consequences, including prolonged ICU stays, increased healthcare costs, and elevated mortality rates, which can range from 20% to 50%, depending on factors such as the underlying health conditions of patients and the presence of multidrug-resistant pathogens[2,3].

Traditionally, VAP is classified into two categories: early-onset, occurring within the first 4 days of mechanical ventilation, and late-onset, occurring after 5 days. Early-onset VAP is typically associated with community-acquired organisms that are more likely to be sensitive to standard antibiotic therapies. Common pathogens in early-onset VAP include Streptococcus pneumoniae (accounting for 15-30% of cases), Hemophilus influenzae (10-20%), and Methicillin-sensitive Staphylococcus aureus (MSSA), which is responsible for approximately 10-15% of cases. In contrast, late-onset VAP is more frequently associated with hospital-acquired, multidrug-resistant (MDR) organisms such as Pseudomonas aeruginosa (20-30%), Acinetobacterbaumannii (10-20%), Methicillin-resistant Staphylococcus aureus (MRSA), and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (15-25%)[4,5].

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However, the clinical utility of this early versus late-onset distinction is increasingly being scrutinized. Emerging evidence suggests that the microbial profiles and antibiotic resistance patterns in VAP may not strictly adhere to this time-based classification[6].

For instance, even in early-onset VAP, multidrug-resistant organisms like MRSA and ESBL-producing bacteria have been reported in up to 10-20% of cases. Factors such as prior antibiotic use, the patient's immune status, and the local prevalence of resistant organisms might play more significant roles in determining the causative pathogens and their susceptibility patterns than the timing of onset alone. As a result, the assumption that early-onset VAP is less severe or easier to treat may lead to suboptimal treatment strategies and patient outcomes[7,8].

This study aims to critically assess whether the classification of VAP as early or late-onset remains a valuable tool in clinical practice. By comparing microbial profiles, antibiotic susceptibility patterns, and patient outcomes, including mortality, across these two categories, we seek to determine if this distinction truly influences clinical decision-making and outcomes. The findings of this research could have important implications for the management of VAP, potentially leading to a more nuanced approach that goes beyond the simplistic early versus late-onset classification, ultimately improving patient care and outcomes in the ICU setting.

METHODOLOGY

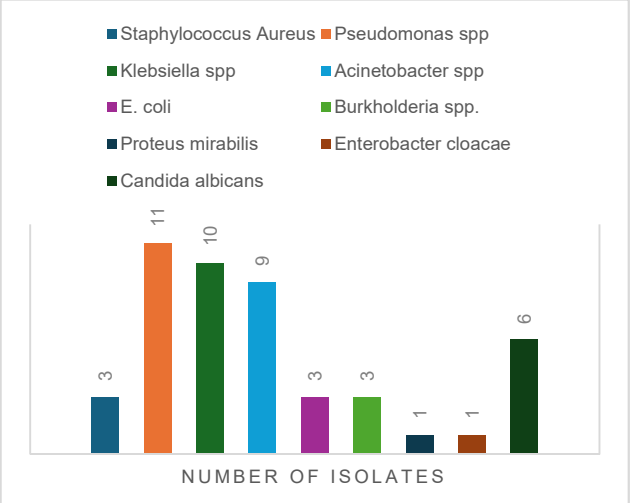
This retrospective clinical audit was done in the surgical ICU (SICU) of Doctors Hospital and Medical Centre, Lahore, Pakistan, over an eighteen-month period from 1st January 2023 to 31st June 2024. Data was collected using non-probability consecutive sampling. After the ethical approval from the Institutional Review Board of the hospital, data was collected from the ICU registers of the anesthesia department and from the digitally saved record of culture samples from the Laboratory of DHMC, Lahore. Exclusion Criteria for this study Patients who have pneumonia on admission, died within 48 hours of admission, and those who developed acute respiratory distress syndrome (ARDS). Patients of both genders (male and female) with an age greater than 15 years and those who were kept on mechanical ventilation for more than 48 hours (about 4 days) were included in this study. Data was analyzed using the IBM SPSS 29.0 software, and an Excel sheet was used to make a table of isolates and their sensitivity to antibiotics. Descriptive statistics like standard deviation and mean are used. One sample t-test was applied. SPSS and Excel sheet files are provided with the text. The P-value was set at <0.05 and a confidence interval of 95% is taken.

RESULTS

A total of 293 patients were put on mechanical ventilation during our study period that meet our inclusion criteria. A total of 46 ventilator associated pneumonias (VAP) were recorded during our study period of 18 months, making the incidence 15.69%. Out of 46 cases, 13 (28.2%) were early-onset VAP and 33 (71.7%) were late-onset VAP. Males being more admitted in our surgical ICU, their number of VAP is also high, that is, 31(67.3%), while females constitute 15(32.6%) cases. We had divided the patients into three age groups: less than 40 years, between 40 and 60 years, and more than 60 years. Less than 40 years old group had 11(23.9%) patients, 40-60 years old age group had 14 patients, and above 60 years old age group constitutes 21(45.6%) cases of VAP. Overall, the most common isolates are Pseudomonas 11(23.9%), Klebsiella 10(21.7%), Acinetobacter 9(19.5%), Candida albicans 6(13%), Burkholderia 3(6.5%), Staphylococcus aureus (3, 6.5%), proteus mirabilis 1(2.2%), and Enterobacter cloacae 1(2.2%); see figure 1. Among the early-onset VAP, the most common isolates were Pseudomonas aeruginosa 4(30.7%), Candida albicans 4(30.7%), Klebsiella pneumonia 2(15.38%), followed by each one of the Acinetobacter, Burkholderia, and E. coli. While in the late-onset VAP, isolates that appeared on tracheal cultures were Acinetobacter 8(24.2%), Klebsiella 8(24.2%), Pseudomonas 7(21.2%), Staphyloccusaureus 3(9.09%), Burkholderia 2(6.06%), Candida 2(6.02%), Proteus mirabilis 1(3.03%), E. coli 1(3.03%) and Enterobacter cloacae 1(3.03%). All of the above details are summarized in Table 1.

Overall, 15(32.6%) patients who developed VAP could not survive, while only 31(67.4%) survived. Among the late-onset VAP cases, 8 (24.2%) out of 33 patients expired, while in early-onset cases, 7(53.8%) patients expired.

Figure 1: Isolates on tracheal cultures after 48 hours of mechanical ventillation



The only gram-positive organism is Staphylococcus aureus, and it is 100% sensitive to vancomycin, levofloxacin, linezolid, teicoplanin, rifampicin, doxycycline, and minocycline, while 66.6% sensitive to gentamicin and chloramphenicol. Almost all gram-negative organisms were sensitive to colistin except one E. coli. All Pseudomonas and Acinetobacter isolates were resistant to carbapenems (100% resistance), while Klebsiella is only 40% (4 out of 10) sensitive to carbapenems, E. coli 50% (1 out of 2), Burkholderia 66.6% (2 out of 3) and Proteus mirabilis was 100% sensitive. Klebsiella is 70% sensitive to chloramphenicol. Minocycline has 100% susceptibility for Acinetobacter, Enterobacter, and Staphylococcus aureus, 60% susceptibility to Klebsiella, and 33.3% susceptibility to Burkholderia. Levofloxacin has a sensitivity of 45.4% for Pseudomonas, 40% for Klebsiella, and 0% for Acinetobacter. Antibiotic susceptibilities are shown in Table 2.

Table 1: General features of the study population.

Characteristics	Features	Early-onset VAP	Late-onset VAP	Total Positive VAP.
Total cases	Classification of VAP	13 (28.26%)	33 (71.7%)	46
Gender	Male	9(69.2%)	22(66.6%)	31(67.3%)
	Female	4(30.7%)	11(33.3%)	15(32.6%)
Mean Age	<40 years	3(23.07%)	8(24.2%)	11(23.9%)
	40-60 years	5(38.4%)	9(27.2%)	14(30.4%)
	>60 years	5(38.4%)	16(48.4%)	21(45.6%)
Isolates in Tracheal Cultures	Staphylococcus Aureus	0	3(9.09%)	3(6.5%)
	Pseudomonas aeruginosa	4(30.7%)	7(21.2%)	11(23.9%)
	Klebsiella pneumonia	2(15.38%)	8(24.2%)	10(21.7%)
	Acinetobacter species	1(7.69%)	8(24.2%)	9(19.5%)
	E. coli	1(7.69%)	1(3.03%)	2(4.34%)
	Burkholderiacepacia	1(7.69%)	2(6.06%)	3(6.52%)
	Proteus mirabilis	0	1(3.03%)	1(2.2%)
	Candida albicans	4(30.7%)	2(6.06%)	6(13.0%)
	Enterobacter cloacae	0	1(3.03%)	1(2.2%)
Outcome of VAP	Survived	6(46.1%)	25(75.7%)	31(67.4%)
	Died	7(53.8%)	8(24.2%)	15(32.6%)

Table 2: Antibiotic susceptibility of each of the isolates from tracheal cultures.

Antibiotics	Merope-num	Imipe-num	Piperacillin-tazobactem	Vancom ycin	Ceftazi dime	Amika-cin	Tobramy cin	Amoxicilin-Clavunate	Cefipime	Collistin	Chlorem-phenicol	Levofloxa-cin	Ofloxa-cin	Ciprofloxa cin	Doxy cycline	Minocycline	Gentamicin	Lineolid	Teicoplanin	RIFAMPI-CIN	Trimethoprim/sulfamethoxazole
Gram positive																					
Staph aureus	-	-	-	S (3/3) 100%	-	-	-	-	-	-	S(2/3) 66.6%	S(1/3) 33.3%	-	-	S(3/3) 100%	S(3/3) 100%	S(2/3) 66.6%	S (3/3) 100%	S(3/3) 100%	S(3/3) 100%	S(1/3) 33.3%
Gram negative																					
Klebsiella-pneumoniae	S(4/10) 40%	S(4/10) 40%	S(4) 40%	-	S(1) 10%	S(4) 40%	S(4) 40%	S(3)30%	-	S (10) 100%	S(7)70%	S(4)40 %	S(4) 40%	S(4) 40%	S(6)60%	S(6)60%	S(4)40%	-	-		0%
Pseudomonas aeruginosa	0%	0%	0%	-	S(2) 18.1%	S(4) 36.3%	S(4) 36.3%	-	S(2) 18.1%	S (11) 100%	-	S(5) 45.4%	S(5) 45.4%	S(2) 18.1%	-	-	-	-	-		0%
Acinetobacter species	0%	0%	0%	-	-	-	S(1) 11.1%	-	-	S (9) 100%	-	0%			S(6) 66.6%	S(9) 100%	S(1) 11.1%	-	-		0%
E. Coli	S(1) 50%	0%	0%	-	-	S(1) 50%	-	-	-	S(1) 50%	S(1) 50%	-			-	-	-	-	-		0%
Burkholderiacepacia	S(2) 66.6%	0%	0%	-	S(1)3 3.3%	-	-	-	-	N/A	1/3 (33.3%)	S (2) 66.6%			-	S(1) 33.3%	-	-	-		0%
Proteus merabilis	S(1) 100%	S(1) 100%	S(1) 100%	-	S(1) 100%	S(1) 100%	S(1) 100%	S(1) 100%	-	S(0/1) 0%		-			-	-	S(1) 100%	-	-		0%
Enterobacter cloacae	S(1) 100%	S(1) 100%	S(1) 100%	-	-	S(1) 100%	S(1) 100%	-	S(1) 100%	S(1) 100%		S(1) 100%	S(1) 100%	S(1) 100%	S(1) 100%	S(1) 100%	S(1) 100%	-	-	-	0%
Candida albicans	-	--	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

DISCUSSION

The cumulative incidence of VAP came out to be 15.69% in our study, which is in accordance with a study done by Wu D, Wu C[9] and Kharel S, Bist A, Mishra SK[10]. The incidence of early-onset VAP is 28.26%, while that of late-onset VAP is 71.78%. These results are in accordance with a study done by Bacha T, Tsegaye N, Tuli W[11], which shows 23.3% incidence of early VAP and 76.67% in late-onset VAP.

In our study, 67.3% of included patients were males, while 32.6% were females. This male predominance may be secondary to being more males admitted in our surgical ICU overall and secondly because there is a component in the X-chromosome that provides immunity to the female population. Male gender is an independent risk factor for VAP[12]. This gender distribution in our study correlates with a study done by Li Y, Liu C[13] in which 79% of the study population was male.

Age greater than 60 years old made 45.6% of included patients in our study. Age is considered an independent risk factor for VAP secondary to reduced physiological functions, including a decrease in immunity, decreased lung elasticity, cough reflex, etc[14]. While there is a study done by Alvina BB, Afzal M, Ali A[15] that showed that old age is not an independent risk factor for VAP and has no effect on mortality.

Our study showed that multi-drug-resistant organisms were responsible mainly for both early and late-onset VAP, and there was no difference in the isolate profiles of the 2 groups irrespective of duration of onset, with the most common being Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacterbaumanni. This study correlates with the study done by Ben Lakhal H, M'Rad A[16]. According to research done in the US, the number of nosocomial infections caused by MDR bacteria came out to be more than 2 million in 2011, with an estimate of 30,000 deaths[1].

Common causative organisms of this study include gram-negative bacteria (GNB) like Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter species, E. coli, and gram-positive bacteria (GPB) like Staph Aureus. These findings correlate with the study done by Feng DY, Zhou YQ et al[17]. In our study, among the 46 VAP patients, the most common organism identified was Pseudomonas aeruginosa 11(23.9%), followed by Klebsiella pneumoniae 10(21.7%), Acinetobacter Baumanni 9(19.5%), Burkholderiacepacia 3(6.5%), Staph Aureus 3(6.5%), E. coli 2(4.3%), Proteus mirabilis 1(2.2%), Enterobacter cloacae 1(2.2%), and Candida albicans 6(13%). So among the organisms causing VAP, GNB (bacteria) constitute 80.3%, while GPB (gram positive bacteria) constitute about 6.5%, and the rest 13% is caused by Candida albicans. This trend correlates with a study done in which 74% of organisms are gram negative and 20% gram positive organisms[18].

A high resistance rate was found against various antibiotics, especially Acinetobacterbaumanni and pseudomonas aeruginosa, which were resistant to all groups of carbapenems, fluoroquinolones, and B lactam drugs. Similarly, there was also an increased incidence of B-lactamase producing bacteria, especially Klebsiella pneumonia (Table 2). The MDR bacteria in Tunisia hospital also followed the same spectrum of antibiotic resistance[19].

In our study, Klebsiella pneumoniae showed 70% sensitivity to chloramphenicol and 40% sensitivity to carbapenems and fluoroquinolones, whereas pseudomonas aeruginosa showed 45.4% sensitivity to levofloxacin and ofloxacin. Almost all the MDR bacteria showed 100% sensitivity to Colistin (Table 2). One strain of E. coli and Proteus mirabilis were resistant even to colistin, which is a globally alarming sign. This is similar to the study done by Xue LY, Gaowa S et al[14]. Staph aureus shows 100% sensitivity to Vancomycin, Linezolid, Tetracyclines, Teicoplanin, and Rifampicin in our study.

This study is done to ensure that intravenous broad-spectrum antibiotics should be initiated as an empirical therapy to which organisms, especially MDR bacteria, should be sensitive to prevent early and late onset of VAP. At the end of our study, we suggest that Colistin-based empirical therapy should be started in the ICUs of our country, where there is a huge incidence of MDR-gram-negative bacteria. Colistin can also be used in combination with an antibiotic like Rifampicin, but according to a randomized control trial done by there was no superiority of Rifampicin plus Colistin combination in having better outcomes in MDR-GNB treatment as compared to Colistin administration alone[20], but synergistic drug combinations (including two or more of the following: polymyxin, amoxicillin/sulbactam, carbapenems, Fosfomycin, tigecycline/minocycline, a rifamycin, and aminoglycoside) is the only current regime to cover colistin resistance[21]. However, a gram-positive cover for treatment against MRSA like Vancomycin, linezolid, or teicoplanin can be added to Colistin for empirical therapy. This is also suggested by a similar study done by Park HJ, Cho JH[22]. This empirical antibiotic therapy will help in reducing the administration of ineffective and inadequate therapies against MDR-GNB and will help in reducing the incidence of early and late-onset VAP, thus decreasing a burden on the healthcare system and being less cumbersome for the patient and his family.

In our study, out of 46 patients, 15 patients died due to VAP. The mortality rate was 32.6%. Mortality rate for early onset VAP was 53.8% (7 patients) and 24.2% (8 patients) in late-onset VAP. This is in comparison to a study done in Portugal[23], where 38.8% and 41.2% mortality rates were found for early and late-onset VAP, respectively.

The shortcomings of our study include 1) a single-center study because results may vary among different centers' 2) a short sample size due to it being a monocentric study. 3) retrospective nature of study.

CONCLUSION

At the end of this study period of 18 months, we conclude that VAP is mainly caused by MDR bacteria, especially Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter Baumanni,

in our settings, irrespective of the duration of onset. There is no significant difference in the prevalence and the resistance pattern of different bacteria depending upon the early and late onset classification. Furthermore, we suggest that broad spectrum MDR cover, including colistin, along with gram positive cover like vancomycin, linezolid, or teicoplanin, should be started as an empirical therapy to prevent the onset of early or late VAP. Further prospective studies of longer durations and multiple centers are required to confirm the findings of our study.

IRB Approval: Permission was taken from Ethical Review Committee of Hospital

Informed consent from Patients: Informed consents were taken from families if any personal data was taken.

Declaration: This is original clinical audit/ research and it is not being published or submitted anywhere else previously for publication.

Authors Contributions: SR: Conception of idea and analysis of data .**US:** Writing the discussion part and data collection. **HS:** writing the introduction part. **SG:** data collection. **AT:** Proof read of the article

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