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Original Article

A PROSPECTIVE OBSERVATIONAL STUDY ON ANTIBIOTIC USAGE TRENDS, RISK FACTORS AND 28 DAYS MORTALITY RATE ASSOCIATED WITH VENTILATOR-ASSOCIATED PNEUMONIA AMONG MEDICAL ICU PATIENTS: INSIGHTS FROM A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: This study was conducted to investigate the antibiotic usage, risk factors and mortality associated with the development of VAP (Ventilator Associated Pneumonia).

Methods: An open–labelled, prospective, observational (case-control) study was carried out for 6 mo in the Department of Critical Care Medicine. Initial screening was done based on inclusion and exclusion criteria and 58 patients were found eligible. The statistical analysis was done using the Chi-Square test and t-test.

Results: The incidence of VAP in our study was 6.07%. Prolonged hospitalisation (p=0.00) and ICU stay (p=0.00) showed a statistically significant association with the development of VAP and they possessed a high risk of carbapenem-resistant organisms in the age group more than 60 years. Colistin therapy alone and/or combined with tigecycline therapy showed 100% survival. SOFA (Sequential Organ Failure Assessment) scoring done before and after VAP diagnosis showed a significant difference (p<0.005). Our study revealed that mortality was high in patients with SOFA score range of 7-9.

Conclusion: The lower incidence of VAP points out the good infection control practices in the ICU (Intensive Care Unit). Late-onset VAP was more prevalent with *Acinetobacter baumannii*. Prolonged hospitalization and ICU stay were the significant risk factors. Colistin therapy alone and/or in combination with tigecycline was the most effective treatment.

Keywords: Ventilator-associated Pneumonia, Mortality rate, Antibiotics, Prescribing pattern, Risk factors

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INTRODUCTION

Patients in the Intensive Care Unit are at risk for dying not only from their critical illness but also from secondary processes such as nosocomial infection. Pneumonia is the second most common nosocomial infection in critically ill patients, affecting 27% of them [1]. Mechanical ventilation accounts for 8-26% of nosocomial pneumonia, termed Ventilator Associated Pneumonia (VAP). VAP is defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation [2]. The mortality attributable to VAP has been reported to range between 27-75 % [3, 4]. World over and especially in India the prevalence of hospital-acquired infections due to MDR (Multi Drug Resistant) pathogens is high. Carbapenem-resistant pathogens, including Acinetobacter and Enterobacteriaceae, are on the rise, further narrowing our treatment options and raising the possibility of treatment failure [5]. Choosing appropriate therapy for VAP includes knowledge of organisms likely to be present, local resistant patterns within the ICU, common rational antibiotic regimens, and rationale for antibiotic de-escalation or stoppage [6]. Initiating early and effective treatment for ventilator-associated pneumonia (VAP) is linked to lower mortality rates. If the initial therapy within the first 48 h is insufficient, even if subsequent therapy is adequate, the mortality rate can be as high as 91%. However, if the empirical therapy is appropriate from the start, the mortality rate can be significantly reduced to below 38%. Delays in the administration of appropriate antibiotic therapy for VAP have been associated with excess mortality [7]. This study focuses on determining the incidence and mortality of VAP, identifying the predisposing factors associated with the development of VAP and analysing patterns of antibiotic usage among medical ICU patients.

MATERIALS AND METHODS

Study design

This was an open–labelled, prospective, observational (case-control) study carried out for 6 mo in a Tertiary Care Hospital. The protocol of the study was approved by the Institutional Human Ethics Committee with proposal number 15/009.

Study population

The calculated sample size was 70. Seventy patients who were admitted to our Medical ICU (>18 years of age, mechanically ventilated for>48 h) were included in our study. Patients who were immune-compromised and who were diagnosed with ventilator-associated tracheobronchitis were excluded from the study. During follow-up, 12 were found to be dropouts (discharged against medical advice) and fifty-eight patients were selected. Patients were allocated into case and control groups based on VAP diagnostic criteria. Twenty-four patients were diagnosed with VAP and taken as cases. The remaining 34 patients were considered control.

Diagnostic criteria for VAP

Presence of progressive or new infiltrate on chest X-ray, along with at least two of the three clinical features (Temperature>38 °C, Leukocytosis or leucopenia, Purulent respiratory secretions), and a positive respiratory culture (with bacterial counts of 106 CFU/ml for endotracheal aspirate or 103 CFU/ml for Broncho alveolar lavage culture) are indicative of ventilator-associated pneumonia [8].

Data collection

Patients who satisfied inclusion and exclusion criteria were included in the study. Consented patients were assessed for SOFA scores within 24 h of ICU admission. Patients were assigned to the control group and case group on the development of VAP.

SOFA [9] was again done for patients in the case group within 24 h of diagnosis of VAP. The following risk factors were documented for the patients in both groups-prior: hospitalization and antibiotic therapy within 90 d, length of hospital stay and ICU stay, re-

intubation, readmission to ICU and duration of ventilation. Antibiotic prescribing patterns were assessed based on the appropriateness of empirical therapy and definite therapy concerning sensitivity reports and the outcome was assessed using the 28 d mortality.

Statistical analysis

Statistical Analysis was done using SPSS 19.0 Version. An unpaired t-test was used to compare SOFA scores between case and control groups. A paired t-test was used to compare SOFA scores of the case group before and after diagnosis of VAP. P-Value<0.05 was considered as Statistically Significant. The chi-square test was used to estimate the association between risk factors and development of VAP.

RESULTS

The number of new VAP cases in our ICU during the study period was 24. The total number of patients at risk for VAP during the study period was estimated to be 395. The incidence of VAP in our study was 6.07%.

Regarding gender, the incidence of VAP was higher among males (75%) than females (25%) and about different age groups the incidence of VAP was highest in patients>60 years of age (50%). 66.7% of the patients had late onset VAP, with an average number of days for onset of VAP around 10 d, while 33.3% (8/24) of the patients had early onset VAP.

The bacteriological profile for VAP in this hospital depicted that 93.93% of gram-negative organisms were the causative agent in VAP while gram-positive organisms were 6.07% seen only in early-onset VAP. Mainly 6 strains of bacteria, among which *Acinetobacter baumannii*(42.42%) was the most prevalent, followed by Klebsiella pneumoniae (33.33). Monomicrobial (single bacteria) infections accounted for 66.6% of patients, whereas polymicrobial (more than one bacteria) infections for 33.33%. Fig. 3 illustrates the resistance and sensitivity patterns of bacterial isolates, highlighting variations based on the production of carbapenems and Extended Spectrum Beta-Lactamase (ESBL). Out of the 24 patients who were on empirical treatment 17% (4/24) received monotherapy, while 83% received combination therapy. In Empirical therapy, 33.33% were Piperacillin/Tazobactam 4.5/2.25g Q6h followed by Meropenem 1g q12h (20.83), Imipenem 100 mg Q8h (12.5), Colistin 4.5mU q12h and Ceftriaxone 1g q8h (12.5%). In definite therapy, Colistin 4.5mU q12h (41.6%) and Colistin+Tigecycline 50 mg (29.17%) were prescribed more compared to other antibiotics. Table 1 describes the Characteristics, Bacteriological Profile and prescribing pattern of antibiotics among VAP patients.

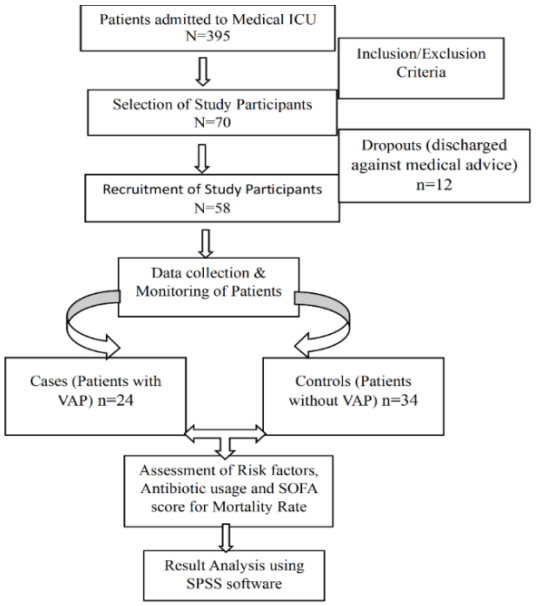

Fig. 1: Flowchart of methodology

Table 1: Characteristics, bacteriological profile and prescribing pattern of antibiotics among Study Participants with VAP

Parameters	Patients with VAP N=24 (%)	Parameters	Patients with VAP N=24(%)
Gender		Age	
Male	18(75)	20 – 40	6(25)
Female	6(25)	40 – 60	6(25)
		>60	12(50)
Onset of VAP		Nature of Bacteria	
Early	8(66.66)	Gram Positive	2(8.33)
Late	16(33.33)	Gram Negative	22(91.67)
Pattern of Bacteria		Pattern of Antibiotics	
Singe	16(66.66)	Single therapy	4(17)
Multiple	8(33.33)	Combination therapy	20(83)
Name of Bacteria		Empirical Antibiotics	
Gram Negative Bacteria	14(58.33)	Meropenem 1g q12h	5(20.83)
Acinetobacter Baumanni	11(45.83)	Colistin 4.5mU q12h	3(12.5)
Klebsiella Pneumoniae	5(20.83)	Ceftriaxone 1g q8h	3(12.5)
Pseudomonas aeruginosa	2(4.16)	Cefotaxime 1g q12h	1(4.16)
E. Coli	1(4.16)	Piperacillin/Tazobactam 4.5/2.25g Q6h	8(33.33)
Gram Postive Bacteria*Streptococcus Pneumoniae*	1(4.16)	Colistin+Tigecycline 50 mg	2(8.33)
		Imipenem 100 mg Q8h	3(12.5)
Staphylococcus aureus		Cefoperazone 1g+sulbactam 0.5g q12h	2(8.33)
Combinations of Polymicrobial		Definite Antibiotics	
A. baumanni and K. pneumoniae	5(20.83)	Meropenem 1g q12h	2(8.33)
K pneumoniae and P. aeruginosa	1(4.16)	Colistin 4.5mU q12h	10(41.6)
P. aeruginosa and A. baumanni	1(4.16)	Ceftriaxone 1g q8h	1(4.16)
		Cefotaxime 1g q12h	1(4.16)
		Piperacillin/Tazobactam 4.5gQ6h	1(4.16)
		Colistin+Tigecycline 50 mg	7(29.17)
		Imipenem-Cilastatin 1000 mg Q8h q12h	1(4.16)

Table 2 reveals that *Acinetobacter Baumann* and *Klebsiella pneumoniae* were more commonly found in late-onset VAP, with prevalences of 62.5% and 56.25%, respectively, compared to early-onset cases. *Acinetobacter Baumann* exhibited a 37.5% resistance rate in early-onset VAP and 40% in late-onset. Furthermore, 54.16% of late-onset and 20.83% of early-onset VAP cases were linked to inappropriate empirical antibiotic therapy. However, the timing of VAP onset did not significantly correlate with the type of organism, its sensitivity, or the use of empirical antibiotic therapy. Additionally, 25% of patients did not receive any empirical antibiotic therapy.

Table 2: Bacteriological profile and empirical therapy between early and late onset of VAP

Parameters	Early onset of VAP N=8 (%)	Late onset of VAP N=16 (%)	P value
Baccterialogical Profile			
Gram Negative Bacteria	4(50)	10(62.5)	0.83
Acinetobacter Baumanni	2(25)	9(56.25)	
Klebsiella Pneumoniae	-	5(31.25)	
Pseudomonas aeruginosa	-	1(6.25)	
E. Coli	1(12.5)	-	
Gram Postive Bacteria			
Streptococcus Pneumoniae	1(12.5)	-	
Staphylococcus aureus			
Sensitivity/Resistant Pattern			
Acinetobacter Baumanni	1/3(12.5/37.5)	6/4(60/40)	0.56
Klebsiella Pneumoniae	1/1(12.5/12.5)	3/6(33.33/66.67)	
Pseudomonas aeruginosa	-	2/3(40/60)	
E. Coli	-	1/0	
Streptococcus pneumoniae	1(12.5)	-	
Staphylococcus aureus	1(12.5)	-	
Empirical Therapy			
Appropriate	-	3(18.75)	0.34
Inappropriate	5(62.5)	10(62.5)	

Table 3 indicates that reintubation is a significant risk factor for VAP in medical ICU patients, with an odds ratio (OR) of 4.42 and a p-value of 0.003. Additionally, prolonged hospital stays and extended ICU admissions were also significant, with ORs of 1.87 ($p<0.01$) and 1.45 ($p<0.01$), respectively, in the development of VAP. While not statistically significant, prior hospitalization and antibiotic use were more frequent in VAP patients than in the control group.

Table 3: Assessment of risk factors associated with VAP

Risk factors	VAP (case) n=24 (%)	Non-VAP (control) n=34(%)	Relative risk	Odds ratio	Confidence interval	p-value
Reintubation*						
Yes	6(25)	1(2.9)	0.346	4.432	0.238-0.503	0.003
No	18(75)	33(97.1)				
Prior hospitalisation						
Yes	5(20.83)	8(23.53)	1.098	1.169	0.509-2.366	1
No	19(79.17)	26(76.47)				
Prior antibiotics						
Yes	4(16.66)	7(20.58)	1.17	1.296	0.52-2.736	1
No	20(83.33)	27(79.42)				
Readmission						
Yes	5(20.83)	2(5.88)	0.522	0.238	0.290-0.940	0.114
No	19(79.17)	32(94.12)				
Hospital Stay*						
<15 d	3(12.5)	7(20.58)	0.133	1.876	0.045-0.398	0.000
>15 d	21(87.5)	27(79.42)				
ICU stays*						
<15 d	12(50)	2(5.88)	0.318	1.452	0.188-0.539	0.000
>15 d	12(50)	32(94.12)				

Table 4 illustrates the sensitivity and resistance of definite therapy among VAP patients. 57.14% of organisms show resistance to Colistin and 62.5% with Colistin+Tigecycline combination therapy followed by other antibiotics. Ceftriaxone and Cefotaxime had 100% sensitivity to the organism.

Table 4: Sensitivity and resistant pattern of definite therapy among VAP patients

Name of the antibiotics	Name of the organism (in numbers)										Total N (%)	
	A. K		P. A		K. P		S. P		E. Coli			
	S	R	S	R	S	R	S	R	S	R	S	R
Colistin 4.5mU q12h	4	3	1	1	-	4	1	-	-	-	6(42.85)	8(57.14)
Colistin+Tigecycline 50 mg	2	3	-	-	1	1	-	1	-	-	3(37.5)	5(62.5)
Meropenem 1g q12h	-	-	-	1	1	-	-	-	-	-	1(50)	1(50)
Imipenem 100 mg Q8h	-	1	-	-	-	1	-	-	-	-	-	2(100)
Ceftriaxone 1g q8h	-	-	1	-	-	-	-	-	1	-	2(100)	-
Cefotaxime 1g q12h	1	-	-	-	1	-	-	-	-	-	2(100)	-

A. K-Acinetobacter Baumanni, P. A-Pseudomonas aeruginosa, K. P-Klebsiella pneumoniae, S. P-Streptococcus Pneumoniae, S-Sensitivity, R-Resistant

In this study, 28 d mortality of VAP was 50% which is shown in table 5. After diagnosing VAP, the mean SOFA score increases from 6+5.5 to 8+6.3. In patients with ventilator-associated pneumonia (VAP), 54.16% had a (SOFA) score between 7 and 9, 25% had a score between 10 and 12, and 16.67% had a score between 0 and 6. None of the patients had a SOFA score above 14. In the context of (SOFA) scores, 75% of the mortality was observed in patients with scores ranging from 0 to 6, while 61.53% of the mortality was associated

with scores between 7 and 9. Fig. 2 presents a comparison of SOFA scores between VAP and non-VAP patients in a medical ICU, showing that 55.88% of non-VAP patients had a score ranging from 0 to 6, 23.53% had a score from 7 to 9, and 20.53% had a score of 10 to 12.

Table 5: Assessment of SOFA score and 28 d mortality rate among VAP patients

SOFA score range (0-24)	Predicted mortality as per SOFA guidelines	VAP n=24 (%)	Observed mortality n=12(%)
0-6	Less than 10%	4(16.67)	3(75)
7-9	15 – 20 %	13(54.16)	8(61.53)
10-12	40 – 50 %	6(25)	1(16.66)
13-14	50 – 60 %	1(4.17)	-
15	More than 80%	-	-
16-24	More than 90%	-	=

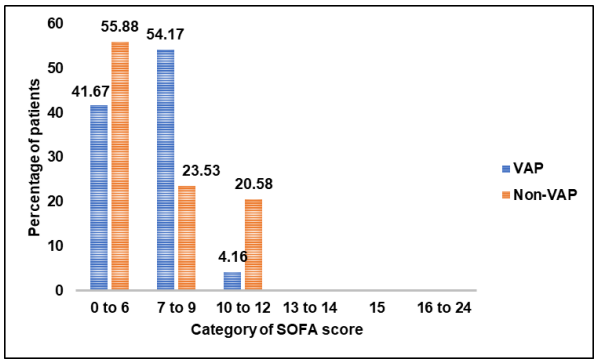

Fig. 2: Comparison of SOFA between VAP and Non-VAP patients in a medical ICU

The study analysed risk factors linked to 28 d mortality in patients with ventilator-associated pneumonia (VAP) and found no significant associations with VAP outcomes. The age factor and Empirical therapy exhibited an odds ratio (OR) of 2.88 and 1.49, respectively, which was not statistically significant. Assessment of Risk factors associated with 28 d mortality is shown in table 6.

Table 6: Assessment of risk factors associated with 28 d mortality among VAP patients

Risk factors	Death n=12 (%)	Survival n=12 (%)	Odds ratio	Confidence interval	p-value
Age					
<60	8(66.66)	5(41.6)	2.88	0.532 to 14.735	0.254
>60	4(33.33)	7(58.33)			
Onset of VAP					
Early	3(25)	4(33.33)	0.467	0.082 – 2.656	0.667
Late	9(75)	8(66.66)			
Empirical therapy					
Yes	4(33.33)	3(25)	1.429	0.271 – 7.518	1.00
No	8(66.66)	9(75)			
Carbapenem sensitivity					
Sensitive	8(66.66)	7(58.33)	0.357	0.068 – 1.879	0.414
Resistant	4(33.33)	55(41.6)			
SOFA score					
Low	3(25)	1(8.33)	3.666	0.323 to 41.592	0.294
High	9(75)	11(91.66)			

DISCUSSION

The overall incidence of ventilator-associated pneumonia (VAP) in our study was 6.07%, which is at the lower spectrum compared to the 15-58% range reported in other studies [10, 11]. The variability in incidence rates can be attributed to multiple factors, including variations in the study population, the efficacy of infection control measures within ICU environments, geographical differences, diagnostic standards, and the hospital's treatment guidelines [12, 13]. Our research indicated a higher prevalence of Ventilator-Associated Pneumonia (VAP) among male patients over the age of 60. This observation aligns with the findings of Neelima Ranjan *et al.*, which reported a greater incidence of VAP in males older than 55 years, with a rate of 57.14% [14]. A review of research from 2004 to 2014 shows a significant presence of gram-negative bacteria in VAP cases, with fig. ranging from 63% to 89%. In Western countries, however, the predominance of gram-positive bacteria may be influenced by specific medical practices and environmental factors [15].

The association between empirical therapy, as well as the bacteriological profile, and the development of Ventilator-Associated Pneumonia (VAP) was evident in our study, which demonstrated that 66.67% of VAP cases were late-onset. Patients subjected to inadequate empirical antibiotic treatment tended to develop late-onset VAP characterized by gram-negative, carbapenem-resistant strains, predominantly Acinetobacter baumannii. In contrast, early-onset VAP was generally attributed to gram-positive, carbapenem-sensitive strains. These findings are in line with the research conducted by Papazian l *et al.*, which identified Pseudomonas aeruginosa as the most frequently isolated pathogen in both early

and late-onset VAP cases [16, 17]. Similarly, Joseph *et al.* found that Acinetobacter spp. and Pseudomonas aeruginosa were the leading causes of late-onset VAP [18].

Our study observed that reintubation was associated with a significantly increased risk of ventilator-associated pneumonia (VAP), aligning with previous research. The limited number of reintubations in our patient cohort, which stood at six, suggests a potential for reduced VAP incidence when compared to larger samples. Factors such as impaired airway reflexes and altered consciousness post-extubation may contribute to the heightened VAP risk upon reintubation [19, 20].

Numerous studies have identified prolonged hospitalization and extended ICU stays as significant predictors of morbidity in patients with VAP [21, 22]. This correlation may be due to the deterioration of patients' clinical conditions over lengthy hospital admissions. Additionally, these factors were linked to an increased risk of encountering carbapenem-resistant organisms in patients older than 60 years. Our observations are corroborated by a study from China by luo *et al.*, which identified a history of pre-ICU admission, hospitalization in the preceding six months, and transfers from other wards or hospitals as key risk factors for VAP development [23].

The microbiological analysis identified six bacterial strains, with gram-negative, carbapenem-resistant bacteria being the most prevalent. With up to 40% of VAP cases being polymicrobial, involving pathogens like Pseudomonas spp., Acinetobacter spp., and Kleb. pneumonia, it becomes imperative to investigate the local microbial flora [24, 25]. There is a growing concern over Acinetobacter baumannii strains that exhibit strong antibiotic resistance, as they have been found contaminating commercial food products and livestock, revealing several environmental channels through which they can spread to humans [26, 27].

In our research, combination antibiotic therapy was administered more frequently than monotherapy, and it was observed that the mortality rate was higher among patients receiving monotherapy compared to those on combination therapy. The data revealed that patients who received appropriate empirical treatment had a 100% survival rate. Conversely, those treated with inappropriate therapy experienced fatalities, and among patients who persisted with antibiotics to which their infections were resistant, the mortality rate was high [28].

Our study primarily analysed antibiotics such as Piperacillin-tazobactam, Meropenem, Imipenem, third-generation cephalosporins (ceftriaxone, cefotaxime), and colistin-either as standalone treatments or in combination with tigecycline. We observed that patients treated exclusively with colistin or in conjunction with tigecycline exhibited a 100% survival rate. These results mirror the findings of Neelima Ranjan *et al.*, where Acinetobacter spp. was frequently isolated, displaying a resistance pattern where the majority were multi-drug resistant, and colistin proved to be exceptionally effective [29]. In definitive therapy scenarios, colistin and tigecycline emerged as the predominant antibiotics [30].

Upon review, it was noted that despite the organisms' sensitivity to carbapenem antibiotics, treatment was initiated with high-end antibiotics such as colistin and tigecycline. This practice may contribute to the emergence of resistant bacterial strains and escalate antibiotic resistance. Remarkably, patients treated with colistin, either alone or in combination with tigecycline, had a 100% survival rate. In contrast, other antibiotics did not result in improvement, nor did they prevent patient mortality. These findings echo the research by Abushanab D *et al.*, which indicated that for early-onset VAP, colistin was the most efficacious antibiotic, followed by piperacillin/tazobactam and imipenem [31].

Assessment using the SOFA score both before and after the diagnosis of VAP indicated a significant difference ($p<0.005$). However, initial SOFA scores taken on the first day for both cases and control groups showed no notable variance. Although higher SOFA scores are typically associated with increased mortality, our findings suggest a substantial mortality risk even at lower SOFA scores [32], specifically within the 0 to 9 range. Sequential assessments using the SOFA score have been identified as reliable indicators of mortality, particularly when conducted on the third and fifth days of patient follow-up [33].

The mortality rate among patients with Ventilator-Associated Pneumonia (VAP) was observed to be 50%. Our study did not find any specific factors that were consistently associated with mortality in VAP cases. However, when examining different age demographics, a higher mortality rate was noted within the 20–40-year age bracket. Additionally, infections caused by carbapenem-sensitive organisms were associated with a higher mortality rate, potentially due to a delay in the diagnosis of VAP [34].

The scope of our study is limited by its execution in a resource-constrained environment, with a relatively small patient cohort suffering from VAP, and its confinement to a single-center setting. Even though there is an increasing prevalence of MDR pathogens in late-onset VAP, knowledge about the susceptibility patterns of the local pathogens should be used as a guide for the choice of antibiotics.

CONCLUSION

Our study highlights the success of stringent infection control measures in the ICU, as evidenced by the reduced VAP rates observed. Despite the small sample size, the correlation between reintubation and VAP incidence in our study underscores the need for vigilant post-extubation monitoring and preventive strategies. The correlation between extended mechanical ventilation and lengthened ICU stays with the onset of VAP suggests these are critical areas for intervention to improve patient outcomes. The prevalence of multidrug-resistant organisms in VAP highlights the necessity for tailored antimicrobial strategies based on regional bacteriological profiles. In both empirical and definite therapy, colistin therapy alone and/or in combination with tigecycline was the most effective treatment. SOFA scoring after VAP diagnosis may help in modifying the treatment options with a better outcome.

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AUTHORS CONTRIBUTIONS

Dr Rama Parthasarathy: Conduction of the project, data analysis and interpretation, Preparation of manuscript submission, revision, Dr. Anita Ann Sunny: preparation of protocol, data input, revision, Data collection and compilation.

CONFLICT OF INTERESTS

Declared none

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