

Early- vs Late-onset Ventilator-associated Pneumonia in Critically Ill Adults: Comparison of Risk Factors, Outcome, and Microbial Profile

Anitha Gunalan¹, Apurba Sankar Sastry², Venkateswaran Ramanathan³, Sujatha Sistla⁴

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is one of the most frequent hospital-acquired infections, which develops in mechanically ventilated patients after 48 hours of mechanical ventilation. The purpose of this study was to determine the incidence rate, various risk factors, microbiological profile, and outcome of early- vs late-onset ventilator-associated pneumonia (VAP) in medical intensive care unit (MICU).

Materials and methods: This prospective study was conducted on 273 patients admitted to the MICU in JIPMER, Puducherry, from October 2018 to September 2019.

Results: The incidence of VAP was 39.59 per 1000 ventilation days of MICU patients (93/273). Of these, 53 (56.9%) patients had early-onset VAP and 40 (43.1%) had late-onset VAP. Multiple logistic regression analysis showed that steroid therapy, supine head position, coma or impaired unconsciousness, tracheostomy, and re-intubation were found to be independent predictors of early- and late-onset VAP, respectively. Most cases of VAP were caused by Gram-negative bacteria (90.6%), with nonfermenters contributing to 61.8%. The most frequent pathogens causing early-onset VAP were *Acinetobacter baumannii* (28.9%) and *Pseudomonas aeruginosa* (20.6%), while in late-onset VAP, *A. baumannii* (32.9%) and *Klebsiella pneumoniae* (21.9%) were the most common. Maximum death rate was seen in patients infected with *Escherichia coli* (50%) and *Stenotrophomonas maltophilia* (38.5%). There was no significant association between the presence of VAP and mortality among the studied population.

Conclusion: The incidence of VAP in our study was high. There were no significant differences in the prevalence of pathogens associated with early-onset or late-onset VAP. Our study shows that early-onset and late-onset VAP have different risk factors, highlighting the need for developing different preventive and therapeutic strategies.

Keywords: Healthcare-associated infections, Intubation, Ventilator, Ventilator-associated pneumonia.

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a nosocomial infection that develops 48 – 72 hours or thereafter following endotracheal intubation and mechanical ventilation (MV) and is not present when the patient is intubated.¹ Ventilator-associated pneumonia is one of the commonest nosocomial infections with an incidence rate ranging from 13 to 51 per 1000 ventilator days.^{2,3} Ventilator-associated pneumonia increases the period of ICU stay by 4–6 days, thereby secondarily increasing the cost of patient management.⁴ Male sex, underlying disease severity, and admission of patients with a history of trauma are various independent risk factors that lead to the development of VAP.⁵ It has been estimated that roughly 50% of antibiotics administered in the ICU are used for the management of VAP cases.⁶

Ventilator-associated pneumonia can be categorized into early and late onset, with early-onset VAP occurring within 96 hours of MV and late-onset VAP occurring after 96 hours of initiation of MV, with the latter being usually caused by multidrug-resistant (MDR) pathogens leading to increased morbidity and mortality.^{1,2} Aerobic Gram-negative bacilli accounts for more than 60% of VAP cases.⁷ *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have emerged as the most important nonfermentative Gram-negative nosocomial pathogens, the management of which is complex because of increasing resistance to antimicrobial agents.⁸ Ventilator-associated pneumonia has a high mortality rate of 25–50%.⁹

^{1,2,4}Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, Tamil Nadu, India

³Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, Tamil Nadu, India

Corresponding Author: Sujatha Sistla, Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, Tamil Nadu, India, Phone: +91 9894058062, e-mail: sujathasistla@gmail.com

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Fagon et al. found that when the diagnosis of VAP was done clinically, it had a false-positive rate of 20–25% and 30–35% false-negative results.¹⁰ To overcome all these difficulties, in 1991, Pugin et al. developed a scoring system that comprises seven clinical parameters and was named as Clinical Pulmonary Infection Score (CPIS).

Table 1: Clinical pulmonary infection score calculation

Assessed parameter	Result	Score
Temperature (°C)	36.5–38.4°C	0
	38.5–38.9°C	1
	≤36 or ≥39°C	2
Leukocytes in blood (cells/mm ³)	4000–11000/mm ³	0
	<4000 or >11000/mm ³	1
	≥500 band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/non-purulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diffuse/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth	1
	Moderate or florid growth AND pathogen consistent with Gram stain	2
Oxygenation status (defined by PaO ₂ :FiO ₂)	>240 or ARDS	0
	≤240 and absence of ARDS	2

A total score of 6 or more suggests VAP. They found that CPIS had a sensitivity and specificity of 93% and 100%, respectively.¹¹

This study aimed to assess the incidence, risk factors, etiological agents, and the associated outcome in detail for effective and proper management of such patients.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Microbiology and Department of General Medicine, JIPMER, after getting approval from Institute Ethics Committee for Human Studies (JIP/IEC/2018/0142). A written consent was taken from all the patients. Patients who were mechanically ventilated for >48 hours ($n = 273$) in medical intensive care unit (MICU) JIPMER from October 2018 to September 2019 were included in this study. Patients admitted to MICU with pneumonia and transferred to JIPMER with a diagnosis of VAP done in other hospitals were excluded. These patients were monitored daily using CPIS criteria (Table 1), and the risk factors, treatment details, and outcome were recorded. The sample (endotracheal aspirate) was taken from the patient and sent to the microbiology laboratory for Gram staining and semiquantitative culture in case of clinical suspicion. Threshold values generally employed for the diagnosis of VAP by quantitative cultures are $\geq 10^5$ CFU/ml for endotracheal aspirates.¹² For semiquantitative culture, a standard loop is taken, and growth more than the tertiary streak is considered as $\geq 10^5$ CFU/mL. Identification of the organism from the clinical sample was done by MALDI-TOF MS (VITEK MS, bioMerieux).

All the entries were done using Epicollect software. Continuous variables like age, duration of hospital stay, duration of stay in the ICU, and duration of MV were expressed as mean with standard deviation. The incidence of VAP was expressed as incidence proportion with 95% confidence interval and also as incidence density of VAP per ventilator days. The etiology was summarized as percentages. Univariate analysis of risk factors was performed, and those found significant by this were assessed for significance by multivariate logistic regression analysis, and the outcome of VAP was expressed as proportion with 95% confidence interval.

Table 2: Age and sex distribution of patients with and without VAP

Parameter	VAP ($n = 93$)	Non-VAP ($n = 180$)	<i>p</i> -value
Age (mean \pm SD)	45.2 \pm 15.9	44.5 \pm 15.09	
Male	62 (66.7%)	123 (68.3%)	0.780
Female	31 (33.3%)	57 (31.7%)	

Table 3: Baseline characteristics of early- and late-onset VAP

Parameter	Types of VAP	
	Early-onset VAP ($n = 53$)	Late-onset VAP ($n = 40$)
<40	17 (32.1%)	15 (37.5%)
40–60	30 (56.6%)	20 (50%)
>60	6 (11.3%)	5 (12.5%)
Age (mean \pm SD)	45.01 \pm 14.4	43.9 \pm 16.1
Male	34 (64.2%)	28 (70%)
Female	19 (35.8%)	12 (30%)
Onset of VAP (days)	3.5 \pm 0.5	6.4 \pm 1.59

Table 4: Univariate analysis of risk factors for VAP

Risk factors	Non-VAP ($n = 180$)	VAP ($n = 93$)	<i>p</i> -value
Duration of MV >5 days	159 (88.3%)	77 (82.7%)	0.205
Diabetes	84 (46.6%)	47 (50.5%)	0.544
Hypertension	91 (50.5%)	47 (50.5%)	0.998
Chronic renal failure	29 (16.1%)	15 (16.1%)	0.997
Steroid therapy	51 (28.3%)	20 (21.5%)	0.223
Supine head position	2 (1.1%)	6 (6.4%)	0.013
Surgery	27 (15%)	16 (17.2%)	0.636
Stress ulcer prophylaxis	180 (100%)	93 (100%)	1
Coma or impaired consciousness	81 (45%)	54 (58%)	0.041
Tracheostomy	25 (13.8%)	23 (24.7%)	0.026
Trauma	17 (9.4%)	9 (9.6%)	0.95
Re-intubation	46 (25.5%)	41 (44%)	0.002

RESULTS

Of the 273 patients, 93 (34.1%) had VAP during the hospital stay, of which 53 (56.9%) patients developed early-onset VAP. The total duration of MV was 2349 days. The incidence of VAP was 39.59 per 1000 ventilator days. Out of the 93 patients, 85 patients (91.4%) had VAP during first 7 days of MV.

Of the 273 study patients, 185 (67.8%) were males and 88 (32.2%) were females. Out of the 93 patients who had VAP, 62 were males and 31 were females. Of these, 32 (34.4%) patients were <40 years of age, 50 (53.8%) patients were between 40 and 60 years, and 11 (11.8%) patients were >60 years. Neither age nor sex was significantly associated with the development of VAP in our study. Age and gender-wise distribution of patients who developed VAP are illustrated in Table 2. Comparison of baseline characteristics between early- and late-onset VAP is denoted in Table 3.

Univariate analysis indicated that tracheostomy, supine head position, coma or impaired consciousness, and re-intubation were found to be associated with VAP (Table 4). Multivariate logistic analysis is shown in Table 5. Steroid therapy, supine head position, coma, or impaired unconsciousness were found to be specific and independent risk factors for the development of early-onset VAP by univariate and multivariate analysis. Tracheostomy and

Table 5: Multivariate logistic regression analysis of risk factors for VAP

Risk factor	Relative risk	p-value	95% confidence interval	
			Lower	Upper
Tracheostomy	1.590062	0.009	1.124223	2.248929
Re-intubation	1.685676	0.001	1.223363	2.322699
Coma or impaired consciousness	1.415385	0.043	1.010791	1.981926
Supine head position	2.284483	<0.001	1.477825	3.531446

Table 6: Etiological agents causing early- and late-onset VAP

Etiological agent	Early-onset VAP n = 97 (%)	Late-onset VAP n = 73 (%)
Gram-negative bacteria	86 (88.7)	68 (93.2)
Non-fermenters	60 (61.9)	44 (60.3)
<i>Acinetobacter baumannii</i>	28 (28.9)	24 (32.9)
<i>Pseudomonas aeruginosa</i>	20 (20.6)	9 (12.3)
<i>Stenotrophomonas maltophilia</i>	6 (6.2)	7 (9.6)
<i>Chryseobacterium indologenes</i>	1 (1)	1 (1.4)
<i>Elizabethkingia</i> spp.	3 (3.1)	2 (2.7)
<i>Pseudomonas</i> spp.	1 (1)	0
<i>Achromobacter denitrificans</i>	1 (1)	0
<i>Delftia acidovorans</i>	0	1 (1.4)
Enterobacterales	26 (26.8)	24 (32.9)
<i>Klebsiella pneumoniae</i>	18 (18.6)	16 (21.9)
<i>Escherichia coli</i>	4 (4.1)	6 (8.2)
<i>Enterobacter</i> spp.	3 (3.1)	0
<i>Proteus mirabilis</i>	0	1 (1.4)
<i>Citrobacter koseri</i>	0	1 (1.4)
<i>Providencia rettgeri</i>	1 (1)	0
Others		
<i>Haemophilus influenzae</i>	1 (1)	0
Gram-positive bacteria	10 (10.3)	5 (6.8)
<i>Staphylococcus aureus</i>	9 (9.3)	5 (6.8)
<i>Streptococcus pneumoniae</i>	1 (1)	0

re-intubation are associated with the development of late-onset VAP by univariate and multivariate analysis.

Of the 93 patients who had VAP, only one patient did not have any bacterial growth in the ETA. In the current study, we have used CPIS criteria for the diagnosis of VAP, according to which a total score of 6 is sufficient to be labeled as a case of VAP. In that one patient, even though culture results were negative, clinical and radiological evidences were present, giving a total score of 6. Ventilator-associated pneumonia was mostly caused by Gram-negative bacteria (90.6%) with nonfermenter contributing to 61.8%. Among the Gram-negative organism causing VAP, *A. baumannii* (30.6%) and *Klebsiella pneumoniae* (20%) were the commonest, and *Staphylococcus aureus* (8.2%) was the commonest among the Gram-positive organism. The causative agents of early- and late-onset VAP are listed in Table 6. Of 93 cases, 32 (34.4%) cases were of monomicrobial in origin, and 60 (64.5%) cases had polymicrobial VAP.

In our study, it was found that the maximum death rate was seen in patients infected with *Escherichia coli* (5/10) and *Stenotrophomonas maltophilia* (5/13). No statistical analysis was attempted since the attributable mortality rate was difficult to

Table 7: Outcome of VAP and non-VAP groups

	Outcome		Total	p-value
	VAP (n = 93) (%)	Non-VAP (n = 180) (%)		
Died	29 (31.2)	48 (26.7)	77	0.432
Recovered	64 (68.8)	132 (73.3)	196	

calculate. Empirical antibiotic therapy was started for VAP patients, and it was seen that 53 patients (56.9%) received inappropriate antibiotic therapy, which was later changed to appropriate antibiotic therapy based on the susceptibility pattern of the isolates. The mortality rate between VAP and non-VAP groups was not statistically significant ($p = 0.432$) (Table 7).

DISCUSSION

The incidence of VAP in our study was high (39.59 episodes per 1000 ventilator days), which was similar to other Indian studies (8.9–46 episodes per 1000 ventilator days).¹³ This possible cause of high incidence rate may be due to a shortage of nursing staffs in the ICU (ideally 1:1 ratio), which would indirectly affect the care given to the patients. Similar to other studies, our study also had increased occurrence of early-onset VAP (56.98%).^{14,15}

These results were higher when compared with a study done by Reham et al., who found that only 9.6% of patients had early-onset VAP, the possible reason for which could be prior administration of antibiotics.¹⁶ In our study, the incidence of VAP was high in males (68.33%), which was not statistically significant ($p = 0.780$). These findings are in line with studies done by Sharpe et al. and Goel et al., who found that VAP was more common among men, but the possible reason for increased incidence of VAP among men was unknown.^{17,18} The mean age group for development of VAP in our study was 45 years. A study by Blot et al. showed that the elderly age group (> 60 years) is more susceptible to the development of VAP. However, our study did not show any statistical difference in age between VAP and non-VAP group.

Analysis of the risk factors is necessary as it renders a theoretical foundation for the effective prevention of VAP. Prior administration of antibiotic therapy, hospitalization of >5 days, MV for >5 days, supine head position, impaired consciousness, burns, stress ulcer prophylaxis, and re-intubation were the various risk factors causing VAP in other studies.^{19–21} In our study, burns were not present in any of the patients, and stress ulcer prophylaxis was administered to all the patients, in both VAP and non-VAP groups; therefore, their significance could not be studied. A finer understanding of these risk factors for the development of VAP is necessary for anticipating the occurrence of VAP and helps in guiding the clinician to implement proper prevention and control measures.

Most cases of VAP (90.6%) were caused by Gram-negative organisms. Among the Gram-negative organisms, 61.8% of VAP were caused by non-fermenters. Of the various organisms causing VAP, *A. baumannii* (30.6%) was the commonest, followed by *K. pneumoniae* (20%) and *P. aeruginosa* (17.1%). Though community-acquired pathogens are more commonly causing early-onset VAP, nonfermenters also have a role in causation of early-onset VAP, especially in cases with prior history of antibiotic exposure and previous hospitalization.¹⁴ However, prior history of antibiotic exposure and previous hospitalization is not taken, which is one of the potential limitations of the study. A few of the community-acquired pathogens like *Haemophilus influenzae* and *Streptococcus*

pneumoniae are fastidious and may not have been recovered even if they were the original causative agent. A study conducted by Joseph et al. a decade earlier from our hospital also reported similar findings where 80.9% of VAP was caused by Gram-negative organisms of which 59.6% were nonfermenters.¹⁴

Numerous studies have centered on the causative agents responsible for the development of VAP and the rate of VAP and its resistance pattern varies depending on the place of study. A survey conducted by Hashemi et al. in Iran showed that 24.6% of VAP was caused by *A. baumannii* followed by *P. aeruginosa* (20.2%).²² A similar study by Rocha et al. in Brazil showed that *P. aeruginosa* (29%) was the commonest organism causing VAP, followed by *S. aureus* (26%) and *Acinetobacter spp.* (18%).²³ In our study, it was seen that 32 (34.4%) patients had monomicrobial growth and 60 (64.51%) patients had polymicrobial VAP. Hejazi et al. reported that 92.59% had polymicrobial VAP and only 7.41% had monomicrobial growth.²⁴ An Indian study by Kapaganty and Pilli reported that 67.9% had monomicrobial growth and 32.1% had polymicrobial VAP.²⁵

In our study, we found that *A. baumannii* and *P. aeruginosa* were the commonest organisms causing early-onset VAP, whereas *A. baumannii* and *K. pneumoniae* were the commonest organisms causing late-onset VAP. A study done by Golia et al. showed that *P. aeruginosa* and *E. coli* were the commonest organism causing both early- and late-onset VAP.²⁶ A study done by Joseph et al. showed that Enterobacteriales, *H. influenzae*, *S. aureus*, *S. pneumoniae*, and *Candida spp.* were more common in early-onset VAP, whereas non-fermenters were common organisms causing late-onset VAP.¹⁴ Few studies showed that Gram-positive gram cocci, primarily *S. aureus* and *S. pneumoniae* are the most commonest organism causing early-onset VAP that is in contrast to our analysis.^{14,27}

Our study highlights the fact that nonfermenting gram-negative bacilli (NFGNB) are now emerging as an important hospital-acquired infection with *P. aeruginosa* and *A. baumannii* being the commonest. These NFGNB are not only present in hospital environment, but are ubiquitously present everywhere and can lead to opportunistic invasive manifestation. Most of these NFGNB vary in their pathogenic potential and are highly resistant to atmospheric conditions favoring them to cause epidemic spread. In resource-limited clinical laboratory, these NFGNB are usually identified with the help of triple-sugar iron (TSI) medium and with Hugh and Leifson O/F (oxidation and fermentation) medium. However, proper identification to species level and monitoring of susceptibility pattern of these nonfermenters is necessary, as they are known for their resistance to commonly used antibiotics, which may advance their proliferation in hospitals and environment, leading to substantial antibiotic treatment and infection control challenges.

In the current study, the mortality rate was 31.2% in the VAP group as compared with 26.7% in the non-VAP group, and we found that maximum death rate was seen in patients infected with *E. coli* (5/10) and *S. maltophilia* (5/13). Although the rates are found to be slightly higher in VAP group, it was not statistically significant. A meta-analysis on the attributable mortality of VAP by Melsen et al. demonstrated that the overall attributable mortality of VAP is 13%.²⁸ Due to the diverse nature of our study population, with contrasting comorbidities and different diagnoses at the time of admission, we cannot remark on VAP being an independent and specific factor for mortality, and the death rate in our study requires further examination.

CONCLUSION

Our study highlights the fact that VAP continues to be an important nosocomial infection and sound knowledge on various risk factors is necessary for anticipating the occurrence of VAP and to implement proper prevention and control measures. Further, our study showed that the pathogens obtained did not follow an early- vs late-onset pattern, therefore, the old concept of differentiating pathogens based on early and late onset may no longer be helpful in starting empirical antibiotic therapy. Our study also emphasizes the fact that nonfermenting Gram-negative bacilli are emerging as important hospital-acquired pathogens with *P. aeruginosa* and *A. baumannii* being the commonest and the identification of these nonfermenters is important as they are usually resistant to commonly used antibiotics leading to unnecessary antibiotic usages and infection control challenges.

AUTHOR'S CONTRIBUTIONS

Dr AG standardized the experiments and performed them, and contributed to the manuscript. Dr SS conceived the idea, supervised all the experiments, validated the results of the experiments, and contributed to the manuscript. Dr ASS and Dr VR reviewed the manuscript.

ORCID

Anitha Gunalan  <https://orcid.org/0000-0002-7779-7877>

Apurba Sankar Sastry  <https://orcid.org/0000-0003-2337-3830>

Venkateswaran Ramanathan  <https://orcid.org/0000-0002-1602-5785>

Sujatha Sistla  <https://orcid.org/0000-0002-4286-6908>

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