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FIVE YEARS' OBSERVATIONAL STUDY ON VENTILATOR ASSOCIATED PNEUMONIA AT A TERTIARY CARE HOSPITAL WITH EMPHASIS ON PRE-COVID-19, COVID-19 AND POST-COVID-19 PERIOD

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is one of the most frequent ICU-acquired infections and a leading cause of death among patients in Intensive Care Unit. The aim of our study is to understand the co-morbidities, bacterial etiological agents, antibiogram and clinical outcome of ventilated patients over a period of 5 years during the pre-COVID-19 (2019), COVID-19 (2020-2021) and post-COVID-19 (2022-2023) period.

Materials and Methods: We conducted a retrospective observational study over a period of 5 years (2019-2023) on ventilated patients of a tertiary care hospital. All adult ventilated patients with more than 48 hours of endotracheal intubation with modified clinical pulmonary infection score >6 were included in the study. We also compared the etiological agents and clinical outcome during the pre-COVID-19 (2019), COVID-19 (2020-2021) and post-COVID-19 (2022-2023) period.

Results: Out of 706 ventilated patients, 93 developed VAP. Males accounted for 77% of the total patients. One-thirds of VAP patients were above 60 years. Most common co-morbidities were hypertension, pneumonia, diabetes and organ system failure. *Acinetobacter baumannii* (44.4%) was the most predominant bacterial isolate in this study, followed by *Klebsiella pneumoniae* (24.5%) and *Pseudomonas aeruginosa* (17%). *Acinetobacter baumannii* remains the commonest isolate during pre-COVID-19, COVID-19 and post COVID-19 period in our ventilated patients. Majority of our *Acinetobacter baumannii* were multi drug resistant (87.2%). Overall mortality rate was 37.6%.

Conclusion: This 5 year study is unique as it portrays the VAP etiological agents, antibiogram and clinical outcome during pre-COVID-19, COVID-19 and post-COVID-19 period. No such Indian study captures these parameters as per the authors knowledge. Implementation of antimicrobial stewardship and strict infection control measures will reduce the risk of MDR pathogens and VAP.

Keywords: Ventilator-associated pneumonia, COVID-19, co-morbidities, antimicrobial resistance.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most frequent ICU-acquired infections and a leading cause of death among patients in Intensive Care Unit.[1] It is defined as pneumonia that develops 48 hours after endotracheal intubation. It is distinguished by the emergence of a new or developing infiltrate in the lungs, systemic infection symptoms such as fever and altered white blood cell count, alterations in the characteristics of the sputum and the identification of the causative agent.[2] It has been associated with increased mortality, longer duration of stay at the hospital and also leads to a greater cost burden among patients.[3] Depending on the risk factors, 10% to 65% of intubated patients get VAP.[4] VAP risk factors include the following: male gender, elderly age, length of hospital stay, patients body positioning, level of consciousness, stress ulcer prophylaxis, use of medications, including sedatives, immunosuppressive drugs and antibiotics; oropharyngeal and gastric colonization, thermal injuries; post-traumatic, post surgical intervention factors, such as emergency intubation, reintubation, tracheostomy, bronchoscopy and inserting a nasogastric tube.[1,5] Associated co-morbidities like multi organ system failure, diabetes mellitus, hypertension, respiratory disease, end stage renal disease, neurological diseases, malignancy and cardiac disease.[6] It is believed that aspirating oropharyngeal secretions containing potentially harmful organisms causes the majority of VAP episodes. It is commonly caused by antibiotic resistant nosocomial organisms like *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* species and *Staphylococcus* species.[4] Furthermore the onset of VAP can be divided into: Early onset VAP which occurs within 5 days of intubation and late onset VAP which occurs after 5 days of intubation. They differ in their pathogenesis, micro-organisms responsible, antibiotic sensitivity, outcome and treatment. Most frequent organisms found in early VAP are normal upper respiratory flora which are not drug resistant. In late onset VAP it is usually *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacterales that are multi drug resistant and Methicillin Resistant *Staphylococcus aureus*.[7] Ventilator associated pneumonia (VAP) still complicates the course of treatment for 8% to 28% of patients on mechanical ventilation, despite significant advancements in respiratory equipment disinfection protocols and techniques for managing ventilator-dependent patients.[8]

VAP incidence was observed to be high among critically ill COVID-19 patients. It was estimated that the attributable mortality of VAP was around 47.6%, and the length of stay doubled for these patients. Enterobacterales were found to be the causative agents for 49.8% of VAP cases in COVID-19 patients, followed by *P. aeruginosa* (24.8%) and *S. aureus* (22%).[9]

This presents an alarming situation of VAP among patients and thus raises an urgent need for further research on the incidence and outcome of VAP to develop cost effective control and preventive measures to reduce the occurrence of VAP and for the better treatment of patients.

Objectives

1. To estimate the co-morbidities for ventilator associated pneumonia.
2. To identify etiology and antimicrobial resistance of ventilator associated pneumonia.
3. To assess the outcome of ventilator associated pneumonia.

MATERIALS AND METHODS

Observational retrospective study was carried out on all ventilated patients admitted in ICU during the period of 5 years (January 2019 to December 2023) by department of Microbiology of a tertiary care Hospital after obtaining institutional ethics committee approval. Patients of both sexes who were on mechanical ventilation for more than 48 hours and modified clinical pulmonary infection score (CPIS) more than 6 were included in the study. [10] The study population were classified into three groups as pre-COVID-19 period (year 2019), COVID-19 period (from 2020 to 2021) and post-COVID-19 period (from 2022 to 2023).

Basic demographic details of patient and clinical outcome were noted from the hospital patient records. The endotracheal aspirate samples of these ventilated patients received in Microbiology Laboratory during the 5 year period from January 2019 to December 2023 showing $>10^5$ colony forming units per mL were analysed.[11] The Gram staining, bacterial identification and antimicrobial susceptibility patterns of the isolate were recorded. Antimicrobial susceptibility testing were performed and interpreted according to respective Clinical and Laboratory Standards Institute (CLSI) guidelines of the study period.[12]

Only bacterial VAP and first episode of microbiologically confirmed VAP were included for the analysis. Multi drug resistant (MDR) was designated to bacterial isolates resistant to atleast one agent in three different antimicrobial categories of drugs.[13]

SARS CoV-2 virus detected in nasopharyngeal and oropharyngeal swabs subjected to Real time reverse transcriptase polymerase chain reaction (RT-PCR) were taken as COVID-I9 positive.[14]

Statistical Analysis: Descriptive data was presented as frequencies and percentages. Chi- square test was used to find the co-morbidities. P value <0.05 is taken as statistically significant. The statistical analysis was performed using SPSS software.

RESULTS

A total of 3,327 patients were admitted in ICU from January 2019 to December 2023. Among them, 706 were on mechanical ventilation and a total of 93 ventilated adult patients fulfilled the eligibility criteria for diagnosis of VAP during the period of 5 years. Males accounted for 77% of the total patients.

One-thirds of VAP patients were above 60 years. The most common co-morbidities were hypertension (34.4%), followed by pneumonia (31.2%), diabetes (28%), Organ system failure (23.7%), AKI/CKD (23.7%), ARDS (20.4%), sepsis (19.4%), COVID (15.1%), COPD (10.8%) and others as shown in [Table 1].

Table 1: Demographic details of the VAP patients

	Pre-COVID-19 (2019) n (%)	COVID-19 (2020-2021) n (%)	Post-COVID-19 (2022-2023) n (%)	Total	Chi square	P value
Total no. of patients in ICU	1104	1307	916	3327	--	--
Total no. of patients on MV	256	336	114	706	60.49	0.0001*
Total no. of patients diagnosed with VAP	32 (12.5)	43 (12.7)	18 (15.7)	93(13.1)	3.546	0.170
Gender						
Female	5 (15.6)	11(25.6)	5 (27.8)	21(22.6)	1.385	0.500
Male	27 (84.4)	32 (74.4)	13 (72.2)	72 (77.4)		
Age in years						
18- 30	5 (15.6)	4 (9.3)	2 (11.1)	11(11.8)	4.312	0.828
31- 40	4 (12.5)	4 (9.3)	3 (16.7)	11(11.8)		
41- 50	5 (15.6)	13 (30.2)	4 (22.2)	22 (23.7)		
51- 60	8 (25)	9 (21)	2 (11.1)	19(20.4)		
>60	10 (31.3)	13 (30.2)	7 (38.9)	30(32.3)		
Co-morbidity#						
COPD	2 (6.3)	2 (4.7)	6 (33.3)	10 (10.8)	11.908	0.003*
Sepsis	8 (25)	7 (16.3)	3 (16.7)	18 (19.4)	0.997	0.607
Organ System Failure	14 (43.8)	7 (16.3)	1(5.6)	22 (23.7)	11.715	0.003*
ARDS	7 (21.9)	6 (14)	6 (33.3)	19 (20.4)	2.997	0.224
Head Trauma	1(3.1)	2 (4.7)	0	3 (3.2)	--	--
Pneumonia	10 (31.3)	14 (32.6)	5 (27.8)	29 (31.2)	0.135	0.935
RTA	1(3.1)	2 (4.7)	1(5.6)	4 (4.3)	0.189	0.910
AKI/CKD	9 (28.1)	11(25.6)	2 (11.1)	22 (23.7)	2.011	0.366
CVA	2 (6.3)	4 (9.3)	2 (11.1)	8 (8.6)	0.396	0.820
Diabetes	6 (18.8)	16 (37.2)	4 (22.2)	26 (28)	3.468	0.177
Hypertension	12 (37.5)	12 (27.9)	8 (44.4)	32 (34.4)	1.744	0.418
Malignancy	0	0	1(5.6)	1 (1)	--	--
COVID	0	14 (32.6)	0	14 (15.1)	--	--
OP Poisoning	1(3.1)	1(2.3)	0	2 (2.2)	--	--
Outcome						
Death	13 (40.6)	15 (34.9)	7 (38.9)	35 (37.6)	3.624	0.459
Discharged	9 (28.1)	17 (39.5)	9 (50)	35 (37.6)		
DAMA	10 (31.3)	11 (25.6)	2 (11.1)	23 (24.7)		

*p-value <0.05 significant

Multiple Co-morbidities were present in a single individual.

MV-Mechanical ventilation, COPD- Chronic obstructive pulmonary disease, ARDS-Acute respiratory distress syndrome, RTA- Road traffic accident, AKI-Acute kidney injury, CKD-Chronic kidney disease, CVA-cerebrovascular accident.

Among the 93 patients diagnosed with VAP, 106 bacterial pathogens were isolated. Gram negative bacilli accounted for 99 (93.4%) and Gram positive cocci accounted for 7 (6.6%) of the total isolates. *Acinetobacter baumannii* (44.4%) was the most common isolate, followed by *Klebsiella pneumoniae* (24.5%), *Pseudomonas aeruginosa* (17%), *Staphylococcus aureus* (5.7%), *Escherichia coli* (3.8%), *Citrobacter* species (2.8%), *Proteus mirabilis* (0.9%) and *Streptococcus pneumoniae* (0.9%).

60 patients (64.5%) had MDR pathogens that caused VAP. Among the Gram negative isolates, 87.2% of *Acinetobacter baumannii*, 42.3% of *Klebsiella pneumoniae* and 16.7% of *Pseudomonas aeruginosa* were MDR. Two isolates out of 3 Citrobacter species (66.7%) were MDR. In the Gram positive cocci isolates, 4 out of 6 isolates of *Staphylococcus aureus* (66.7%) were MRSA. Antimicrobial resistance pattern (AMR) of bacterial isolates of all 106 isolates of VAP cases is shown in [Table 2].

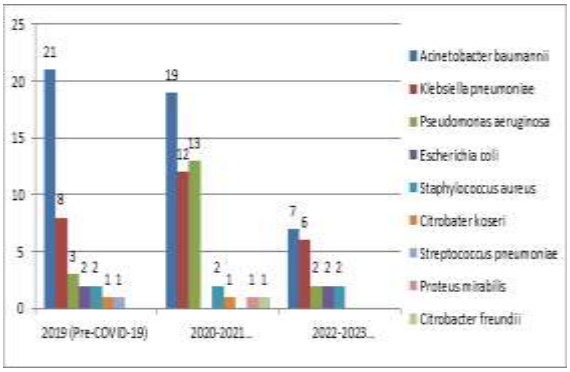

Figure 1: shows the distribution of bacterial isolates during the pre-COVID-19, COVID-19 and post-COVID-19 period.

Table 2: Antimicrobial resistance pattern of bacterial isolates of VAP cases.

Organisms (n)	Ceftriaxone n(%)	Ceftazidime n(%)	Cefe-pime n(%)	Gentamicin n(%)	Amikacin n(%)	Cipro-floxacin n(%)	Levo-floxacin n(%)	Piperacillin-Tazobactam n(%)	Mero-penem n(%)	Imipenem n(%)
Acinetobacter baumannii (47)	45 (95.7)	41 (87.2)	38 (80.8)	40 (85.1)	40 (85.1)	42 (89.4)	36 (76.6)	39 (82.9)	40 (85.1)	37 (78.7)
Klebsiella pneumoniae (26)	23 (88.5)	23 (88.5)	21 (80.8)	18 (69.2)	18 (69.2)	22 (84.6)	21 (80.8)	15 (57.7)	12 (46.1)	7 (26.9)
Pseudomonas aeruginosa (18)	IR* (100)	5 (27.8)	2 (11.1)	5 (27.8)	3 (16.7)	3 (16.7)	3 (16.7)	2 (11.1)	3 (16.7)	3 (16.7)
Escherichia coli (4)	3 (75.0)	3 (75.0)	2 (50.0)	0 (0.0)	0 (0.0)	3 (75.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)
Citrobacter koseri (2)	2 (100)	2 (100)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)
Citrobacter freundii (1)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Proteus mirabilis (1)	1 (100)	1 (100)	1 (100)	0 (0.0)	0 (0.0)	1 (100)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)

Organisms (n)	Cefoxitin n(%)	Gentamicin n(%)	Ofloxacin n(%)	Levofloxacin n(%)	Azithromycin n(%)	Clindamycin n(%)
Staphylococcus aureus (6)	4 (66.7)	3 (50)	4 (66.7)	4 (66.7)	2 (33.3)	2 (33.3)
Streptococcus pneumoniae (1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*IR-intrinsic resistance

Table 3: Distribution of antimicrobial resistance pattern of *Acinetobacter baumannii* and *Klebsiella pneumoniae* during the pre-COVID-19, COVID-19 and post-COVID-19 periods

Period (Total)	Ceftriaxone % (n)	Ceftazidime % (n)	Cefe-pime % (n)	Gentamicin % (n)	Amikacin % (n)	Cipro-floxacin % (n)	Levo-floxacin % (n)	Piperacillin-Tazobactam % (n)	Mero-penem % (n)	Imipenem % (n)
Acinetobacter baumannii										
Pre-COVID-19 (21)	90.4 (19)	85.7 (18)	76.1 (16)	80.9 (17)	80.9 (17)	90.4 (19)	71.4 (15)	76.1 (16)	80.9 (17)	71.4 (15)
COVID-19 (19)	100 (19)	94.7 (18)	89.5 (17)	94.7 (18)	94.7 (18)	94.7 (18)	84.2 (16)	94.7 (18)	94.7 (18)	89.5 (17)
Post-COVID-19 (07)	100 (07)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)	71.4 (05)
p-value	0.629	0.377	0.499	0.258	0.258	0.226	0.486	0.261	0.258	0.404
Klebsiella pneumoniae										
Pre-COVID-19 (08)	87.5 (07)	87.5 (07)	87.5 (07)	75 (06)	75 (06)	100 (08)	100 (08)	62.5 (05)	50 (04)	12.5 (01)
COVID-19 (12)	83.3 (10)	83.3 (10)	83.3 (10)	66.7 (08)	66.7 (08)	66.7 (08)	66.7 (08)	58.3 (07)	41.7 (05)	25 (03)
Post-COVID-19 (06)	100 (06)	100 (06)	66.7 (04)	66.7 (04)	66.7 (04)	100 (06)	83.3 (05)	50 (03)	50 (03)	50 (03)
p-value	0.577	0.577	0.098	0.914	0.914	0.238	0.070	0.849	0.598	0.398

There was no difference in significance during pre-COVID-19, COVID-19 and post-COVID-19 period with clinical outcome (p value: 0.459). Duration of hospital stay had a significant association with clinical outcome (0.000).

Table 4: Correlation of demographic details with clinical outcome of VAP cases.

Variables	CLINICAL OUTCOME- Mean (Std. Deviation)			p VALUE
	Death	Discharged	DAMA	
Age	53.23 (13.89)	47.23 (16.68)	56.09 (13.38)	0.069
Duration of hospital stay (in days)	11.31 (9.206)	23.77 (12.76)	8.78 (4.7)	0.000*

*p-value <0.05 significant

DISCUSSION

This study is unique as per the literature search, no Indian study portrays the co-morbidities, AMR patterns of bacterial isolates and clinical outcome during pre-COVID-19, COVID-19 and post-COVID-19 period. Males accounted for 77% of the total patients. Such high incidence is also observed in many studies worldwide.[15,16] One-thirds (33.3%) of VAP patients were above 60 years. Bimodal peak levels after 59 years of age and also another peak at 18-28 years was noted in another study.[17] Advancing age is usually associated with various co-morbidities, hence incidence of VAP is high.

Patients included in this study had an increased incidence of underlying co-morbidities like hypertension, pneumonia, diabetes, organ system failure, renal dysfunction, sepsis, COVID-19 and COPD. A long term study also showed that COPD, hypertension and diabetes mellitus were the three most common co-morbidities seen in the 338 ventilated patients over duration of 10 years.[18] During the pre-COVID-19 period, organ system failure, hypertension and pneumonia were the most predominant co-morbidity noted. During the COVID-19 period, diabetes mellitus, pneumonia and renal dysfunction were very common. In the post-COVID-19 period, hypertension, ARDS, COPD and pneumonia were of high prevalence among the co-morbidities noted. Pneumonia in combination with hypertension or diabetes seems to be the commonest co-morbidity during all the phases. In the same context, a previous study conducted showed diabetes, hypertension and chest diseases were the commonest co-morbidities associated in COVID-19 ill ventilated patients and these patients required prolonged duration of mechanical ventilation in agreement with our study.[13]

Other interesting point is the varied etiological pattern of ICU microorganisms associated with VAP. Microorganisms causing VAP varies according to many factors like duration of mechanical ventilation, length of hospital stay, empirical antibiotic policy and local ICU flora. *Acinetobacter baumannii* (44.4%) was the most predominant bacterial isolate in this study, followed by *Klebsiella pneumoniae* (24.5%) and *Pseudomonas aeruginosa* (17%). These three Gram negative bacilli constituted the majority bacterial pathogens in our VAP patients. These results agrees with a previous study which showed *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophila* and *Pseudomonas aeruginosa* were the commonest isolates among 190 VAP patients.[19] In contrast *Acinetobacter baumannii* constituted only a small fraction (less than 2.6%) among VAP cases during a 10 years study period from 2014-2024 in Spain. It is claimed in their study that ICU is free of MDR *Acinetobacter* and *Staphylococcus aureus* because of strict antimicrobial policy implemented by antimicrobial stewardship program team.[20]

During the COVID-19 period, *Acinetobacter baumannii* followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the dominant pathogens in this study. On the other hand, the main core pathogens during COVID-19 were Enterobacterales (48%) followed by non-fermenters among VAP cases in France.[21] *Acinetobacter baumannii* remains the commonest isolate during pre-COVID-19, COVID-19 and post COVID-19 period in our ventilated patients. This is a cause for concern as *Acinetobacter baumannii* is usually MDR and poses a significant threat in the ICU thereby prolonging the duration of treatment, usuage of reserve drugs, increased hospital stay in turn leading to increasing morbidity and mortality.

Gram positive cocci accounted for 6.6% of the total isolates. MRSA constituted 66.6% of all *Staphylococcus aureus*. A 10 year surveillance study on VAP also showed out of 4.6% *Staphylococcus aureus*, 70% were methicillin resistant.[22]

Majority of our *Acinetobacter baumannii* were MDR (87.2%). The main hard core bacterial isolate *Acinetobacter baumannii* showed 95.7% resistance to third generation cephalosporins, 80.8% resistance to fourth generation cephalosporins, 85.1% resistance to aminoglycosides, 89.4% resistance to ciprofloxacin, 82.9% resistance to beta lactam-betalactamase inhibitor combination and 85.1% resistance to Meropenem. Similar resistance patterns was also seen in other Indian study. [18] *Klebsiella pneumoniae* showed high level resistance to third generation cephalosporins, fourth generation cephalosporins, aminoglycosides, ciprofloxacin, but less resistance was seen towards beta-lactam beta-lactamase inhibitor combination and carbapenems. These hospital acquired superbugs pose a serious warning threat causing a real problem in ICU. On the other hand, *Pseudomonas aeruginosa* was sensitive to most of the antibiotics in our study. We observed that among the 18 isolates of *Pseudomonas aeruginosa*, the incidence of *Pseudomonas aeruginosa* during the COVID-19 phase (72.2%) was relatively high compared to the pre (16.7%) and post-COVID-19 period (11.1%). Similar results was seen among 568 SARS-CoV-2 infected ventilated patients that *Pseudomonas aeruginosa* was the most frequent etiological agent.[23]

In the present study, overall mortality rate was 37.6%. During COVID-19 period mortality rate was 34.9%. Our study did not show significant differences between pre-COVID-19, COVID-19 and post-COVID-19 period with clinical outcome (0.459). Crude mortality rate was around 33.6% in a similar study and showed a decreasing trend with all three periods (pre-COVID-19, COVID-19 and post-COVID-19) because of use of adequate empirical antibiotics.[20] Prolonged ventilation and increased duration of hospital stay has a significant effect on patient outcome.

CONCLUSION

In this study, more knowledge was gained on the etiological agents and their antibiotic resistance pattern during the three periods (pre-COVID-19, COVID-19 and post-COVID-19). Our study showed that duration of hospital stay had a direct effect on the clinical outcome of the patient. *Acinetobacter baumannii* remains the predominant MDR bacterial isolate in all the three periods. Such analysis makes it important to the physician to start empirical antibiotics and adequately manage as well as limit the spread of MDR with proper infection control measures to prevent VAP. Implementation of antimicrobial stewardship and strict infection control measures will reduce the risk of MDR pathogens and VAP.

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