Original Research Article

Microbiology, risk factors and clinical outcome of Ventilator associated pneumonia at tertiary care Cancer hospital

Aarti R Sangale[1*], Vivek Bhat[2], Sanjay Biswas[3], Amruta Ashok Tikhile[4]

[1]Assistant Professor, Department of Microbiology, LTMMC & GH, Sion, Mumbai, Maharashtra, INDIA.
[2,3]Professor and Consultant, Advanced Center for Treatment Research and Education in Cancer, Tata Memorial Hospital, Mumbai, Maharashtra, INDIA.
[4]Registrar Microbiologist, Sahyadri Speciality Labs, Corporate Office, S N. 89 & 90, Plot No. 54, Lokmanya Colony, Kothrud, Pune 411038, Maharashtra, INDIA.
Email: draarti85@gmail.com

Abstract

Background: VAP is a subgroup of healthcare associated infections (HCAI's) is one of the leading causes of death contributing to morbidity and mortality in ventilated patients. Aggressive antineoplastic chemotherapy makes Cancer patients more susceptible to such infections resulting in high mortality. Knowledge of pathogens associated with VAP and their antimicrobial susceptibility patterns including multidrug resistant (MDR) organisms, risk factors help in selection of appropriate initial antibiotic therapy in these critical cases. **Aim And Objective:** The objectives of this study were to determine microbiology, risk factors and clinical outcome of VAP patients and to determine their antimicrobial susceptibility pattern including MDR isolates in a tertiary cancer centre. **Materials And Methods:** This is a 6 months qualitative observational study carried out at a tertiary care cancer hospital in Mumbai. All nondirect bronchoalveolar lavage (NDBAL)specimens from patients with a clinical suspicion of VAP sent from the critical care unit to the department of microbiology were processed as per standard laboratory procedures. All isolates were identified to species level and an antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method and/or the VITEK 2 automated identification and susceptibility system, according to Clinical and Laboratory Standards Institute guidelines. Results: The study comprised 40 patients: 25(62.5%) males and 15(37.50%) females. A total of 31 isolates of which 30 (96.77%) were Gram negative and one (3.22%) was Gram positive of which Acinetobacter baumannii (45.16%), Klebsiella pneumoniae (19.36%) and Pseudomonas aeruginosa (16.12%) were the commonest. Of gram-negative bacilli, multidrug-resistant organisms constituted 87.50% and were susceptible to colistin. Most of the VAP patients belong to the age groups of > 45 years (50%). And overall mortality associated with VAP was 67.5%. Mortality was high in cases with PCT values > 0.5ng/ml ,50% of deaths had single or combination of these comorbidities and more deaths were observed in patients with hematolymphoid malignancies **Conclusions:** VAP is associated with pathogens, such as A. baumannii, K. pneumoniae and P. aeruginosa in our setting. Multidrug resistant organisms constituted 87.50% of Gram negatives. VAP was higher in patients with comorbid conditions. The crude mortality rate associated with VAP was 67.5% Patients with longer duration of ventilation were at a higher risk for infection with MDR pathogens.

Keywords: Multidrug-resistant organisms, Nondirect bronchoalveolar lavage, Ventilator-associated pneumonia.

[*]**Address for Correspondence:**
Dr Aarti R Sangale, Assistant Professor, Department of Microbiology, LTMMC & GH, Sion, Mumbai, Maharashtra, INDIA.
Email: draarti85@gmail.com

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Ventilator associated pneumonia (VAP) is a subgroup of healthcare associated infections (HCAI's) and it is a critical device associated infection (DAI) observed in intensive care unit (ICU) setting.[1] It is one of the leading causes of death contributing to morbidity and mortality in ventilated patients.[2] Its incidence ranges from 6 % to 52 % according to western[3,4] and 9 %to 58% according to Indian literature.[5,6,7,8] The most common pathogens are Gram negative bacteria namely *Acinetobacter baumanii, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and Gram positive bacteria such as methicillin resistant

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Staphylococcus aureus (MRSA) reported from western as well as from Indian literature.[3,7,8] Mortality rates associatred are 0 % to 54% from general hospital[7,8,9]while in immunocompromised patients it is 73.3% to 76% as per western literature.[10.,11] Severity of underlying diseases, Aggressive antineoplastic chemotherapy exposure to invasive procedures results in high mortality in cancer patients.[12]

AIMS AND OBJECTIVES: The objectives of this study were to determine microbiology, risk factors and clinical outcome of VAP patients and to determine their antimicrobial susceptibility pattern including MDR isolates.

MATERIALS AND METHODS

This is Prospective observational non interventional study conducted in Medical ICU of tertiary care cancer hospital over six months (1st June 2014 through 30th November 2014) and was approved by Institutional Ethics Committee. All patients with clinical and radiological signs suggestive of pneumonia on admission or within 48 hour of mechanical ventilation and clinic-radiological evidence with alternative diagnosis other than VAP were excluded from the study All patients included in the study were monitored at frequent intervals and the clinical parameters were recorded from bedside charts included age, gender, case number, unit, diagnosis, co-morbidities, name and date of surgery, date of admission to hospital and in ICU, duration of mechanical ventilation, endotracheal tube or tracheostomy, duration of mechanical ventilation, antibiotic therapy. The organisms isolated by quantitative culture of the NDBAL from VAP patients were identified based on standard microbiological techniques.[13] The susceptibility of the clinical isolates to some routinely used antibiotics was determined by the Kirby-Bauer disk diffusion method[14]. Qualitative data was represented in form of frequency, percentage and graphs. SPSS Version 22 was used for the analysis.

Criteria for diagnosis of ventilator-associated pneumonia: All NDBAL from patients who were included in the study according to inclusion criteria and were diagnosed based on clinical and radiological criteria stated by Centres for Disease control and prevention[15] Based on these criteria, 40 of 97 enrolled patients were diagnosed with VAP.

RESULTS

There were 97 patients enrolled with the clinical suspicion of VAP and Forty (41.2%) patients were diagnosed as VAP this included 25(62.5%) males and 15(37.50%) females. Of these 40 patients 8 (20%) patients were in the age group of <15 years,4(10%) was in age group of 16-30 years,6(15%) patients in the age group of 31-45 years,12(30%) patients in the age group of 46-60 years, and 10(25%) patients in the age group of >60years. The highest number of patients were from the cases with haematolymphoid malignancy 09 (22.6%) followed by gastrointestinal malignancies 06(15%).Head and neck services comprised of 05 (12.5%) and thoracic malignancies of 05(12.4%) cases. Of the 40 samples, 21 cases showed significant bacterial growth on culture with $> 10^5$ cfu/ml. Of this 16 cases with monomicrobial growth and 5 with polymicrobial growth. There was a total of 31 isolates of which 30 (96.77%) were Gram negative and one (3.22%) was Gram positive.

Table 1 show the Distribution of microorganisms isolated from the NDBAL samples.

Table 1: Distribution of Organisms

Organisms	Frequency	Percentages (%)
Acinetobacter baumanii	14	45.16
Klebsiella pneumoniae	06	19.36
Pseudomonas aeruginosa	05	16.12
Shewanella putrifaciens	01	03.22
Enterobacter cloacae	01	03.22
Elizabethkingia meningoseptica	01	03.22
Burkholderia cepacia	01	03.22
Serratia marcescens	01	03.22
Enterococcus spp.	01	03.22
Total	**31**	**100**

Acinetobacter baumanii was commonest isolate followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

Table 02 shows antimicrobial susceptibility pattern of Gram negative isolates.

Table 2: Antimicrobial susceptibility pattern of Gram-negative isolates

Isolates / Antimicrobials	Susceptibility	*Acinetobacter baumanii*	*Klebsiella Pneumoniae*	*Pseudomonas Aeruginosa*	*Shewanella Putrifaciens*	*Burkholderia cepacia*	*Enterobacter cloacae*	*Eliza. Meningosepticа*	*Serratia marcescens*
		N=14	N=06	N=05	N=01	N=1	N=1	N=1	N=1
Amikacin	R	14	3	1	0	0	1	0	0
		100.0%	50%	23.1%	0.0%	0.0%	100.0%	0.0%	0.0%
	S	0	3	4	1	1	0	1	1
		0.0%	50%	76.9%	100.0%	100.0%	0.0%	100.0%	100.0%
Gentamicin	R	14	5	1	0	1	1	1	0
		100.0%	83.33%	23.1%	0.0%	100.0%	100.0%	100.0%	0.0%
	S	0	1	4	1	0	0	0	1
		0.0%	16.67%	76.9%	100.0%	0.0%	0.0%	0.0%	100.0%
Tobramycin	R	14	NA	1	0	1	1	1	0
		100.0%	NA	23.1%	0.0%	100.0%	100.0%	100.0%	0.0%
	S	0	NA	4	1	0	0	0	1
		0.0%	NA	76.9%	100.0%	0.0%	0.0%	0.0%	100.0%
Netilmicin	R	13	4	1	0	1	1	1	0
		92.86%	66.67%	23.1%	0.0%	100.0%	100.0%	100.0%	0.0%
	S	1	2	4	1	0	0	0	1
		7.14%	33.33%	76.9%	100.0%	0.0%	0.0%	0.0%	100.0%
Ceftazidime	R	14	06	2	0	1	1	1	0
		100.0%	100.0%	40%	0.0%	100.0%	100.0%	100.0%	0.0%
	S	0	0	3	1	0	0	0	1
		0.0%	0.0%	60%	100.0%	0.0%	0.0%	0.0%	100.0%
Cefotaxime	R	14	06	NA	NA	NA	1	NA	0
		100.0%	100.0%	NA	NA	NA	100.0%		0.0%
	S	0	0	NA	NA	NA	0		1
		0.0%	0.0%	NA	NA	NA	0.0%	NA	100.0%
Cefoperozone sulbactum	R	14	05	2	0	0	1	0	0
		100%	83.33%	40%	0.0%	0.0%	100.0%	0.0%	0.0%
	S	0	1	3	1	1	0	1	1
		0.0%	16.67%	60%	100.0%	100.0%	0.0%	100.0%	100.0%
Piperacillin tazobactum	R	14	05	2	0	0	1	0	0
		100.0%	83.33%	40%	0.0%	0.0%	100.0%	0.0%	0.0%
	S	0	1	3	1	1	0	1	1
		0.0%	16.67%	60%	100.0%	100.0%	0.0%	100.0%	100.0%
Ciprofloxacin	R	14	05	2	0	0	1	0	0
		100.0%	83.33%	40%	0.0%	0.0%	100.0%	0.0%	0.0%
	S	0	1	3	1	1	0	1	1
		0.0%	16.67%	60%	100.0%	100.0%	0.0%	100.0%	100.0%
Imipenem	R	14	4	1	1	1	1	1	0
		100.0%	66.67%	23.1%	100.0%	100.0%	100.0%	100.0%	0.0%
	S	0	2	4	0	0	0	0	1
		0.0%	33.33%	76.9%	0.0%	0.0%	0.0%	0.0%	100.0%
Meropenem	R	14	4	1	1	1	1	1	0
		100.0%	66.67%	23.1%	100.0%	100.0%	100.0%	100.0%	0.0%
	S	0	2	4	0	0	0	0	1
		0.0%	33.33%	76.9%	0.0%	0.0%	0.0%	0.0%	100.0%
Colistin	R	0	0	0	0	0	0	0	1
		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
	S	14	06	05	1	1	1	1	0
		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	0.0%

S: Sensitive, R: Resistant.

Note: The isolates with intermediate susceptibility were considered as resistant.

Vancomycin resistant *Enterococcus* was isolated in one case which was observed resistant to teicoplanin, penicillin and ciprofloxacin. Majority of cases with VAP were in patients ventilated for longer than 4 days. This was not statistically significant (p-value = 0.067). The absolute numbers of males were higher than females. The difference was not statistically significant (p-value = 0.114). Most of the patients belong to the age groups of > 45 years (50%).The VAP was found increasing with age of patients and it found statistically significant. (p- value=0.673).
These included 17(42.5%) cases of early onset and 23(57.5%) cases of late onset VAP.

Table 3: Distribution of organisms and onset of VAP.

Organism	Early Onset	Late Onset	Total
Acinetobacter baumanii	2	12	14
Klebsiella pneumoniae	3	3	6
Pseudomonas aeruginosa	2	3	5
Burkholderia cepacia	0	1	1
Enterobacter cloacae	0	1	1
Elizabethkingia meningoseptica	1	0	1
Shewanella putrifaciens	0	1	1
Serratia marcescens	0	1	1
Enterococcus spp.	1	0	1

Outcome in VAP cases was as follows: Overall mortality associated with VAP was 67.5% (27out of 40). This was highest in patients from hematolymphoid service. More number of deaths was seen in paediatric hematolymphoid service (87.5%) and all patients with adult hematology died of VAP. In both services highest cases were of acute lymphocytic leukemia of B cell origin. The 27 cases that died included 12 (44.44%) males and 15 (55.56%) females. The number of patients with late onset VAP who died was 14 (51.9%). Mortality as per organism isolated were evaluated and it was found that *Acinetobacter baumanii* was isolated from 9 (33.3%) patients, *Pseudomons aeruginosa* was isolated from 4 (14.81%) and *Klebsialla pneumoniae* from 3 (11.11%) patients.
Serum procalcitonin (PCT) results were available in 26 cases.

Table 4: Serum procalcitonin (PCT) values and VAP outcome.

PCT value	Alive	Death	Total
less than 0.5ng/ml	1	5	6
>0.5ng/ml and <2ng/ml	1	6	7
more than 2ng/ml	4	9	13

This is a quantitative enzyme linked fluorescent assay.
Out of these 26 patients,13 patients had elevated serum PCT values > 2 ng/ml in the range of 2.15 ng/ml to 37 ng/ml (p value- 0.447) Sensitivity of PCT and cultures was 60% and this had a positive predictive value of 69.23%. but this association was not found to be statistically significant (p value= 0.428)

DISCUSSION

Ventilator associated pneumonia (VAP) is an important cause of illness resulting in prolongation of hospital and ICU stay and increase in the cost of critical care. The combination of impaired host defence and continuous exposure of lower respiratory tract to pathogens through the endotracheal tube increases chances of development of VAP. Prevention of VAP depends on basic infection control practices for successful outcomes in critically ill patients.[4]

Gender Distribution of cases: In our study, The VAP rate was higher in males 26 (52.5%) than in females 21(47.5%) but the study duration being small statistical interpretation is not of significance (p value= 0.114). Sharpe *et al.*,[16] and Joseph *et al.*,[6] found significantly higher VAP in males as compared to females.

Age distribution of cases: In this study, VAP rate was highest in age group of 46-60 (30%) and age group > 60 (25%) years. Although the VAP cases were higher in older age and this was not statistically significant. (p value= 0.673).
A study conducted by Dey *et al.*,[17] also showed that significantly higher VAP acquired in 46-60year age group. Old age, underlying chronic lung disease, previous antibiotic exposure was associated with higher risk for developing VAP reported in studies.[18,19]

Service wise distribution of VAP cases: In our study, the highest number of patients belonged to hematolymphoid, thoracic and gastrointestinal services. Groeger *et al.*,[20] also found that VAP was highest in hematolymphoid malignanacy than solid tumour group. Being cancer hospital, Intensive Care Unit admits more patients with hematolymphoid malignancies than solid tumour cases. These patients are on aggressive chemotherapy regimens, have low neutrophil count and may develop drug toxicity. They are intubated for respiratory distress, stay in the ICU for long duration on mechanical ventilation, all these factors render them prone to developing VAP.

Microbiology of VAP: The common organisms isolated from cases with VAP were *Acinetobacter baumanii* followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. In a Meta- analysis by Arabi Y *et al.*,[1] 41-92% VAP episodes were caused by Gram negative bacilli,

Pseudomonas aeruginosa (9-52%) followed by *Acinetobacter* spp. (0-36%), while 6-58% by Gram positive cocci.

Study by Chandrakanth C et[21] al, reported that Gram negative organisms account for 89% of VAP. Chawla *et al.*,[22] in their study also found that 87% of patients with VAP had Gram negative organisms. Similar findings were reported by Dey *et al.*,[17] Rajshekhar at *et al.*,[23]and Goel *et al.*,[24] where *Acinetobacter baumannii* was the commonest organism causing VAP followed by *Pseudomonas aeruginosa*. All Indian data shows Gram negative predominance. This can be linked with the colonisation of gut and exposure to antimicrobials. Also critically ill patients are on broad spectrum empirical antibiotics which causes selection pressures on these colonisers for emergence of resistant strains of gram negative pathogens. [25,26] Worldwide data indicate that in western countries Gram positives predominate. Potential reasons include the use of indwelling catheters, local environmental conditions and the administration of specific antibiotic agents, especially as prophylaxis.

Microbial aetiology of early Vs. late onset VAP: *In this study, Acinetobacter baumanii was the most common isolate in late onset VAP* important factors being prior antibiotic therapy and current hospitalization of average 11.5 days. *A prospective study* done by Saed *et al.*[27] Rello *et al.* [28], supported association of *Acinetobacter baumanii* with prolonged ventilation and late onset VAP. Of the 30 Gram negative isolates, 27 were multidrug resistant organisms recovered from 23 patients. Of these 23 patients, 21 had received broad spectrum empirical antimicrobial agents like amikacin, cefoperazone sulbactam, piperacillin tazobactam, and meropenem in various combinations along with antifungal. (P=0.22), 20 had undergone a recent curative or reconstructive surgical procedures (p=0.064), 19 had hospitalisation of more than 5 days (p=0.540) and 17 had received mechanical ventilation for more than 4 days(p=0.004).

Therefore, prolonged mechanical ventilation with exposure to ICU environment and microflora has been shown to increase the VAP rate with multidrug resistant organisms. Empirical broad spectrum antimicrobial agents and invasive procedures can also contribute to high VAP rates but this association was not found to be significant in this study possibly due to a small sample size.

Serum Procalcitonin (PCT): Of the 40 VAP patients procalcitonin levels were available in 26 patients of thses 13 patients had elevated serum PCT values >2 ng/ml in the range of 2.15 ng/ml to 37 ng/ml, out of which 9 died. Mortality was high in cases with PCT values > 0.5ng/ml and 13 cases that died had PCT values indicative of severe sepsis. Halim *et al.*,[29] reported that, increased serum PCT level is an important diagnostic tool for VAP and the serum PCT levels can predict the outcome in VAP patients, but in our study, we could not establish this significance (p value = 0.447).

Association between comorbidity and VAP: out of 40 clinically diagnosed VAP cases 20 (50%) had single or combination of these comorbidities. In our study, there was statistically significant correlation between comorbid condition and development of Ventilator associated pneumonia. (p value= 0.0076).

Impact of VAP on outcome: Of the 40 cases with VAP 27 died, more deaths were observed in patients with hematolymphoid malignancies. Groeger *et al.*,[20] observed 76% mortality out of which 41% were from leukemia group 20% from lymphoma group 39% were from solid tumour group. Out of 27deaths, there were 13(48.1%) cases with early onset VAP and 14(51.9%) deaths with late onset VAP. It was observed that more number of deaths were seen in late onset VAP. However, this association was not statistically significant (p-value= 0.361). Similar findings were reported in studies undertaken by Panwar *et al.*[7], and Mukhopadhyay *et al.*,[30] where mortality rate were found to be 37% and 61.9% respectively which showed an increase with the duration of mechanical ventilation. Robust Antimicrobial Stewardship programs involving pharmacists, physicians and other healthcare providers to optimize antibiotic selection, dose, and duration thereby increasing efficacy in targeting causative pathogens for the best clinical outcome is the way forward.

CONCLUSIONS

Microbiology of Ventilator associated pneumonia: Gram negative organisms such as *Acinetobacter baumannii, Klebsiella pneumonia, Pseudomonas aeruginosa* were the most common microorganisms associated with VAP. Multidrug resistant organisms constituted 87.50% of Gram negatives.

Risk factors: VAP was higher in patients with comorbid conditions (p=0.000076). The crude mortality rate associated with VAP was 67.5% (p=0.005). Patients with longer duration of ventilation were at a higher risk for infection with MDR pathogens. (p=0.005)

PCT for diagnosis: Serum procalcitonin is useful indicator of early VAP but was not found statistically significant.

There is a need to explore simple approaches like the care bundle. Implementation of this brought about a reduction in VAP rates.

Antimicrobial stewardship programs need urgent consideration to control the growing numbers of multidrug resistant organisms in critical care units.

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