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Original Research Article

A prospective study on clinical profile, severity, microbiology, and outcome of patients with ventilator associated infective complications admitted in intensive care unit of a tertiary care hospital

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ABSTRACT

Background: Mechanical ventilation epitomizes intensive care medicine. Ventilator-associated complications are mainly Ventilator associated respiratory infections (VARI); These are a major cause of concern in the intensive care units (ICUs) worldwide, especially in developing countries. VARI includes patients with ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). The clinical profile, severity, microbiology, and outcomes of such infections is not well described in Eastern India.

Objective: The primary objective of the study was to study the risk factors, severity scoring, microbiological profile and 28 days outcome of patients admitted in intensive care unit of our hospital. Secondary objective of our study was to find out any correlation between risk factors, severity scoring, microbiological profile, and outcome of patients with VAT and VAP admitted in intensive care unit of our hospital.

Materials and Methods: This was a prospective observational study done in the ICU of a tertiary care centre in eastern India. A total 50 patients of clinically, microbiologically and/or radiologically diagnosed case of VAP and VAT were included in the study. A structured data collection proforma was prepared and data collection was done. Raw data was tabulated and analysed

Results: 66% of our patients were male, Smoking was the commonest addiction(24%), VARI developed early with 17% on Day 3, 72% developed VARI within 5 days of ventilation. 16% had history of recent admission, Diabetes and hypertension were the commonest comorbidities. 58% of the patients developed VAP, the median SOFA score in VAP was 6 also similar in VAT. Patients with neurological diseases had the maximum number of VAT and VAP. Klebsiella pneumoniae was the commonest organism causing VAT (42%) while Acinetobacter Baumannii was commonest to cause VAP (44%). 51% of VAP patients were on volume control mode, while it was 52% of VAT patients. Most isolates are MDR pathogens with intermediate sensitivity to Polymyxin being most common (66%) 1 isolate was pan resistant. Mortality was 58% for VAP and 19% in VAT. Both Klebsiella and Acinetobacter accounts for 41% death in VAP group, in VAT group Klebsiella was commonest however no statistical significance with other organism.

Conclusion: Gram negative bacteria were the predominant cause of VAT and VAP, Acinetobacter and Klebsiella are the commonest organisms. Most Isolates are MDR with intermediate sensitivity to Polymyxins. Median SOFA scores were the same in both. Mortality was high in VAP group. Volume control mode was predominant mode of ventilation, Neurological causes was predominant cause that leads to ventilation and subsequent VARI.

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1. Introduction

Mechanical ventilation epitomizes intensive care medicine. Patients in the intensive care unit (ICU) are at risk for dying not only from their critical illness but also from secondary processes such as nosocomial infection. Ventilator associated infective complications are mainly Ventilator associated respiratory infections (VARI). VARI includes Ventilator associated tracheobronchitis (VAT) and Ventilator associated pneumonia (VAP).^{1–3}

The information regarding VAT incidence is lacking and complicated in parts since the definition remains controversial. Ventilator-associated pneumonia (VAP) is reported to be the most common device-associated nosocomial infection acquired among patients who are mechanically ventilated in the Intensive Care Unit (ICU). The international nosocomial infection control consortium (INICC) data suggests a VAP incidence as high as 13.6/1000 mechanical ventilation (MV) days in developing countries.⁴ The occurrence of VAP in Asian

countries is much higher, and ranges from 3.5 to 46 infections/1000 MV days.⁵ Intubated patients may have rates of pneumonia 7 to 21- fold higher than patients without a respiratory therapy device. Infection rates are twice as high in large teaching hospitals as compared with smaller institutions.⁶ Different scoring systems are available to assess the severity of patients admitted in ICU. Acute Physiology and Chronic Health Evaluation (APACHE) II& III Score, Clinical Pulmonary Infection Score (CPIS), Sequential organ failure assessment score (SOFA) are few of them. Microbiological diagnosis remains cornerstone in initiating treatment of VARIs. However, establishing microbiological diagnosis for patients with pneumonia is always great challenge. The major thrust in management of pneumonia is based on covering the most likely organisms which is intimately related to different risk factors of pneumonia which again depends on the site of acquisition. Various risk factors have been shown to be associated with the risk of infection with Multidrug resistant (MDR) pathogen. Some of them are prior antibiotics use within 90 days, Septic shock at the time of diagnosis of VAP, ARDS preceding VAP, five or more days of hospitalization prior to occurrence of VAP, Acute renal replacement therapy prior to VAP onset.⁷

A recent report presented by a panel of experts from ten Asian countries suggested that the prevalence of MDR pathogens is rising in Asian countries, and *Acinetobacter baumannii*–*calcoaceticus* complex is emerging as a major pathogen in most of these ICUs.⁸ Another Indian study reported that most cases of VAP found in their tertiary level ICU were caused by

Gram-negative bacteria, (80.9%) such as *Pseudomonas aeruginosa* (21.3%) and *A. baumannii* (21.3%).⁹

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Other organisms includes *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Stenotrophomonas* spp, *Burkholderia* spp, *Legionella*, different fungi like *Aspergillus*, *Mucormycosis*.

However data regarding risk factors, severity, microbiological profile and outcome of patients with VAP and VAT is lacking from Eastern India. Our study aimed to investigate the above mentioned parameters in a tertiary care hospital in Eastern India.

2. Materials and Methods

1. Study Area: Intensive care unit of Apollo Gleneagles Hospital, Kolkata. (AGHL)
2. Study population: Patients admitted in ICU of AGHL who are diagnosed with VAT/VAP.
3. Sample Size: 50
4. Study design: Observational Study.
5. Study Duration: 12 months.

2.1. Inclusion criteria

1. Adult 18 years or older.
2. Clinically, microbiologically and/or radiologically diagnosed case of VAT admitted in ICU.
3. Clinically, and/or microbiologically diagnosed case of VAP admitted in ICU.

2.2. Exclusion criteria

1. Age <18 years.
2. Patients of Community acquired pneumonia admitted in ICU.
3. Patient unwilling to participate in the study.
4. Patient diagnosed with VAP/VAT from outside hospital, subsequently transferred to ICU of AGHL.

2.3. Methodology

Measurements are recorded at the time of diagnosis of VAT/VAP among patients admitted in ICU using a structured proforma. Appropriate microbiological samples are collected at the time of diagnosis and sent for analysis. 28-day outcome after diagnosis was assessed.

2.3.1. Study variables: Risk factors included

1. Demographic Data: Age, Sex, Addiction.
2. Comorbidities: Diabetes, hypothyroidism, Obstructive airway disease, immunocompromised states, malignancy, Obstructive sleep apnoea, coronary artery disease, cerebrovascular diseases, Chronic kidney disease, Gastro oesophageal reflux disease.
3. History of trauma: Central nervous system, Chest, Abdomen, Skeletal trauma.
4. Medications within last 3 months: Anti diabetics oral or injectable, hormonal supplements, antiplatelets,

Antibiotics, chemotherapy, Proton pump inhibitors, steroids, immunosuppressives.

5. Number of days on ventilator, Predominant mode of ventilation (Volume control, pressure control, spontaneous, SIMV+pressure support).

Severity of the disease was calculated using Sequential organ failure score (SOFA) scoring system using standard web-based software (MDCalc).

3. Results

Total 50 patients were included in this study, results are described as VAP group that includes patients with diagnosis of ventilator associated pneumonia (n=29), VAT group that includes patients with diagnosis of ventilator associated tracheobronchitis (n=21) and Overall group that include both VAP and VAT group. (n=50)

In overall (Figure 1) and VAP (Table 1) group most of the subjects are above 65 years, however in VAT group (Table 2) 76.2% subjects are below 65 years. Mean age in VAP is 66 and VAT is 52 (p 0.044, unpaired t test). Most of the participants were male in all 3 groups. Smoking and alcohol was the commonest addiction. In overall group 46% patients were ventilated for less than 5 days. In VAP group 37.9% were ventilated for <5 days, in VAT group the percentage was 57.1%. Median ventilation days in all three groups were 4 days. No statistical significant differences were seen in these three groups regarding ventilation days. In all groups majority of the patients did not have recent admission history in last 3 months. In all groups hypertension was the predominant co-morbidity followed by Diabetes mellitus. (Figure 2). Among patients who developed VAIC 44% had a primary neurological diagnosis which includes ischaemic CVA, Intra cranial haemorrhage, Sub arachnoid haemorrhage, meningitis, brain contusion, Traumatic brain injury etc, followed by musculoskeletal diseases including skeletal injury following road traffic accident, hip surgery, spine surgery, long bone fracture etc, followed by a primary respiratory disease including COPD, Lung fibrosis, Diffuse alveolar haemorrhage, post viral infection (Table 4). Median SOFA score was 6 in overall, VAP and VAP group. Figure 4 demonstrates the mean SOFA score.

The comparisons Between age and ventilator parameters are given in table 3. Samples sent for microbiological analysis includes Endotracheal aspirate, tracheal aspirate and bronchoalveolar lavage (Figure 5). In overall group Acinetobacter Baumannii and Klebsiella pneumonia are the commonest organisms (Figure 6). In VAP group Acinetobacter Baumannii was the predominant organism, followed by Klebsiella pneumoniae.(Figure 7). In VAT group Klebsiella pneumoniae was the predominant organism followed by Acinetobacter Baumannii.(Figure 8). The overall antibiotics sensitivity pattern is given in

Figure 9. Acinetobacter baumannii (n=20) and Klebsiella pneumonia (n=20) are the commonest organism in our study. Majority of isolates were multi drug resistant, 2 isolates of Klebsiella pneumonia were pan drug resistant. All of Acinetobacter isolates were intermediate sensitive to colistin(as per CLSI 2021 guidelines), only 1 among those 20 isolates were susceptible to carbapenems (Figure 10). Among 20 Klebsiella pneumoniae isolates 2 were pan drug resistant, rest 18 were intermediate sensitive to colistin(as per CLSI 2021 guidelines),only 2 were sensitive to carbapenems (Figure 11). Apart from respiratory samples in 32% patients had positive blood cultures and 4% had positive urine cultures. The organism pattern in blood cultures are given in Figure 12. Sensitivity patterns were similar to respiratory isolates.

Outcome analysis: overall patient outcome was measured as death, discharged or still admitted till 28th day. Outcomes are shown in Figure 13. In VAP group mortality was 58.6%, in VAT group 19% which was statistically significant (p=.005). (table 4,5)

Analysis of outcome with other clinical and ventilator parameters is given in Table 6.

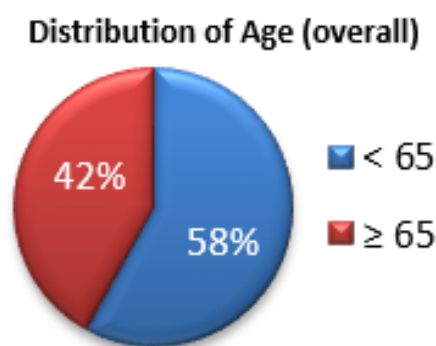


Figure 1: Distribution of age (overall)

Table 1: Age distribution in VAP group

Age	Frequency	Percent
< 65	13	44.8
≥ 65	16	55.2
Total	29	100.0

Table 2: Age distribution in VAT group

Age	Frequency	Percent
< 65	16	76.2
≥ 65	5	23.8
Total	21	100.0

Table 3:

Variable	Group	Statistics	p value	Significance	Test used
AGE	VAP(29)	61.55 ± 18.39 66 (20 - 93)	0.044	Significant	Unpaired t test
	VAT(21)	50.52 ± 18.89 52 (21 - 85)			
Day of Vent	VAP(29)	4.48 ± 2.72 3 (2 - 12)	0.286	Not Significant	
	VAT(21)	5.1 ± 3.19 4 (2 - 16)			
Resp rate	VAP(29)	22.21 ± 4.03 22 (15 - 30)	0.176	Not Significant	
	VAT(21)	20.76 ± 2.93 22 (16 - 28)			
Tidal volume	VAP(29)	380 ± 53.12 380 (240 - 490)	0.167	Not Significant	Mann-Whitney U Test
	VAT(21)	400.48 ± 32.94 400 (350 - 480)			
PEEP	VAP(29)	6.03 ± 1.86 6 (5 - 14)	0.098	Not Significant	
	VAT(21)	5.67 ± 1.62 5 (5 - 12)			
Peak Pressure	VAP(29)	24.07 ± 9.18 22 (12 - 50)	0.458	Not Significant	
	VAT(21)	24.71 ± 6.88 22 (18 - 40)			
FiO2 (%)	VAP(29)	44.31 ± 10.75 40 (35 - 80)	0.66	Not Significant	
	VAT(21)	43.33 ± 6.77 40 (35 - 60)			

Table 4: Outcome analysis in VAP and VAT group

Outcome * Diagnosis Crosstabulation					
Outcome	Diagnosis	N	VAP	VAT	Total
			Death	Count	17
	Row %		81.0%	19.0%	100.0%
	Col %		58.6%	19.0%	42.0%
Hospitalized/Discharged	Count	12	17	29	
	Row %		41.4%	58.6%	100.0%
	Col %		41.4%	81.0%	58.0%
Total	Count	29	21	50	
	Row %		58.0%	42.0%	100.0%
	% within Diagnosis		100.0%	100.0%	100.0%
Chi-Square Tests					
Pearson Chi-Square	Value	p value	Significance		
	7.830 ^a	.005	Significant		

Table 5: Outcome in VAP group

Outcome	Frequency	Percent
Death	17	58.6
Discharged	9	31.0
Still Hospitalized	3	10.3

Table 6: Outcome in VAT group

Outcome	Frequency	Percent
Death	4	19.0
Discharged	10	47.6
Hospitalized	7	33.3

Table 7: Analysis of clinical and ventilator parameters with outcome..

Variable	Statistics	Death	Discharge	Total	p value	Significance	
Age	Mean ± SD	64.38 ±17.37	54.95 ± 19.81	56.92 ± 19.22	0.155	Not Significant	Mann-Whitney U Test
	Median (Min - Max)	65 (33 - 93)	64 (20 - 85)	62 (20 - 93)			
Day of Vent	Mean ± SD	4.71 ± 3.02	3.79 ± 1.44	4.74 ± 2.91	0.707	Not Significant	
	Median (Min - Max)	3 (2 - 12)	4 (2 - 7)	4 (2 - 16)			
SOFA Score	Mean ± SD	8.19 ± 3.41	5.68 ± 1.29	6.64 ± 2.84	0.004	Significant	Unpaired t test
	Median (Min - Max)	7 (3 - 15)	6 (3 - 8)	6 (3 - 15)			
Resp rate	Mean ± SD	22.43 ± 3.82	21.37 ± 3.34	21.6 ± 3.65	0.358	Not Significant	
	Median (Min - Max)	22 (17 - 30)	22 (16 - 30)	22 (15 - 30)			
Tidal volume	Mean ± SD	387.62 ± 53	387.89 ± 47.44	388.6 ± 46.47	0.36	Not Significant	
	Median (Min - Max)	380 (280 - 490)	400 (240 - 450)	395 (240 - 490)			
PEEP	Mean ± SD	6.14 ± 1.93	6 ± 1.94	5.88 ± 1.76	0.171	Not Significant	Mann-Whitney U Test
	Median (Min - Max)	6 (5 - 14)	5 (5 - 12)	5 (5 - 14)			
Peak Pressure	Mean ± SD	24.57 ± 8.73	24.63 ± 8.78	24.34 ± 8.22	0.817	Not Significant	
	Median (Min - Max)	24 (12 - 46)	22 (15 - 50)	22 (12 - 50)			
FiO2 (%)	Mean ± SD	46.19 ± 10.6	43.95 ± 9.06	43.9 ± 9.22	0.353	Not Significant	
	Median (Min - Max)	40 (35 - 80)	40 (35 - 65)	40(35 - 80)			

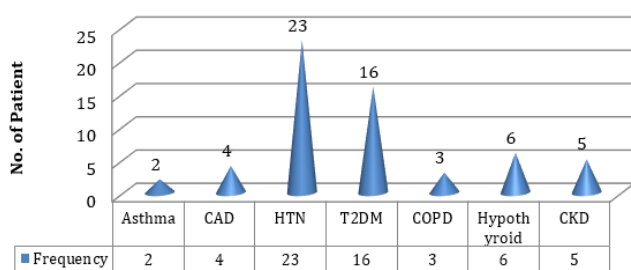


Figure 2:

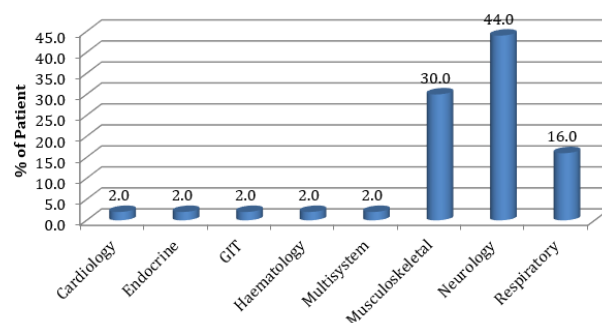


Figure 3: Distribution of primary system

4. Discussion

Pneumonia and Bronchitis are the most common Hospital acquired infection in ICU.¹⁰ Among ICU infections ventilator-associated remains one of the major causes of mortality and morbidity. Ventilator-associated tracheobronchitis is considered as an intermediate condition between bacterial colonization and VAP. VAT and VAP share similar clinical presentation and microbiological

diagnostic criteria, diagnosis of VAP however requires presence of new infiltrate on chest imaging.¹¹

In this observational study we have studied at total of 50 patients with VAT/VAP admitted in ICU. Total duration of our study was one year, Patients have been diagnosed with ventilator-associated infection (VARI) by the primary physician or intensivist. Different clinical details of those

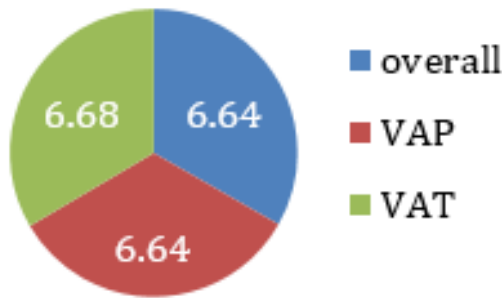


Figure 4: SOFA

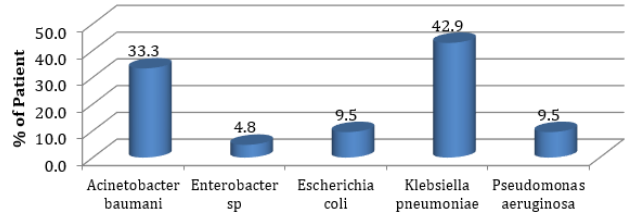


Figure 8: Distribution of Organism in VAT

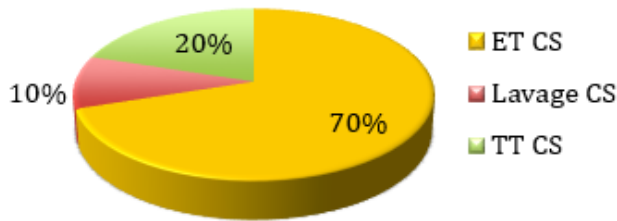


Figure 5: Distribution of sample

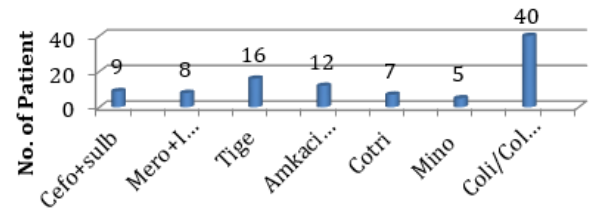


Figure 9: Overall antibiotics sensitivity pattern

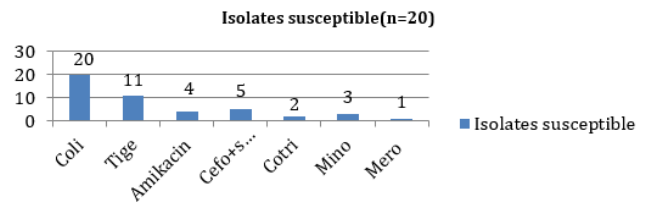


Figure 10: Sensitivity pattern for Acinetobacter baumannii

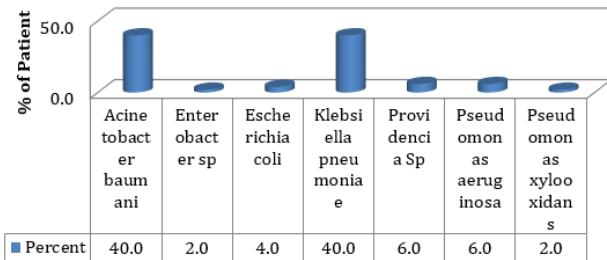


Figure 6: Distribution of organism (overall)

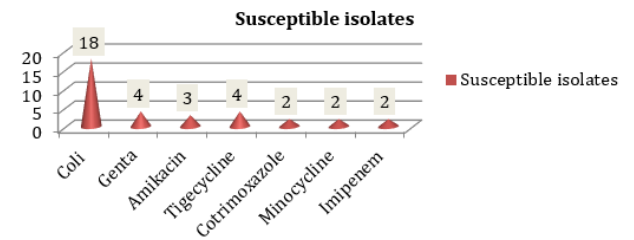


Figure 11: Sensitivity pattern of Klebsiella pneumoniae

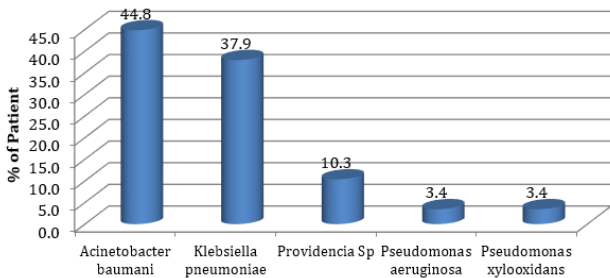


Figure 7: Distribution of organism in VAP

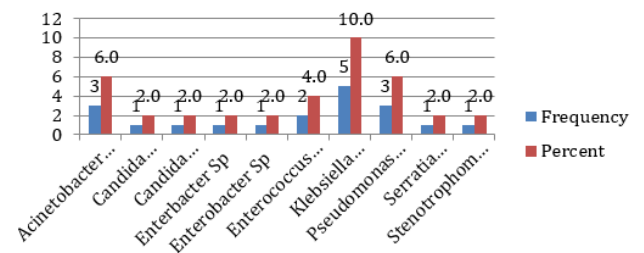


Figure 12: Distribution of organisms in blood cultures

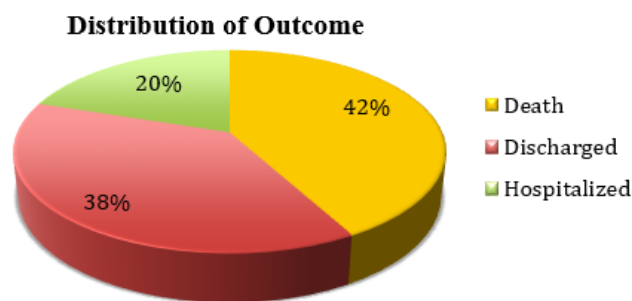


Figure 13: Distribution of outcome

patients were studied using a preformed proforma and then tabulation was done, and results were analysed.

In our study we have seen that the mean age for VAP was 66 years and for VAT it was 52 years, the difference was statistically significant ($p=0.044$). The findings corroborate with the study done by Gadani et al¹² where advanced age was an important risk factor for development of VAP. But et al in a retrospective study of 147 patients showed that the average age of patients with VAP was 69.9 plus minus 15.9 years.¹³ Liu et al¹⁴ in their study have shown that the likelihood of VAP increases more than 1.15 fold with every 1 year increase in the age, they have postulated the causes may be gradual decline in physiological function of respiration, gradual atrophy of the respiratory muscle the gradual decrease of elasticity of lung tissue, protective cough reflex getting weak and also immune function of the elderly is also decreased with age, long-term malnutrition may also precipitate VAP.

While no statistical significant difference was observed mostly the patients were male. In their study Forel et al have found that mostly patients who developed VAP were male, in our study our finding was similar over there was no statistical significance was found in VAP or VAT regarding gender.¹⁵ Difference in risk of VAP between women and men may be related to difference in sex hormone, gender-related gene polymorphism on drug immune response, the distribution of infectious pathogen between men and women may be also different and the complications between men and women may be also different.¹⁶

The 2013 CDC definition which 2015 update was used while diagnosing cases of VAP, the clinical criteria we have used for diagnosis of VAT was like the criteria used by Nseir et al in their study.¹⁷ Also, the criteria we used matches with the criteria used by Craven et al.¹⁸ They have studied 188 mixed ICU patients who are intubated for more than 48 hours they used clinical criteria comprising of at least two clinical criteria (fever, Leucocytosis, or purulent sputum) for diagnosis of VAT and additional persistent infiltrates for diagnosis of VAP.

Papazian et al in their study has evaluated Different techniques for obtaining microbial samples and

analysing them for diagnosis of VAP and establishing a microbiological criterion. They have studied bronchoscopic techniques and non bronchoscopic techniques in diagnosis of VAP. Our present study is similar with the microbiological criteria used by Papazian et al.¹⁹

An Egyptian retrospective study has shown that patients with VAP have a significant long ICU stay than those without VAP.²⁰ Mechanical ventilation for more than two weeks was also a risk factor for VAP in ICU patients.²¹ In our study 62.1% of the patients of VAP were ventilated for more than 5 days in VAT group most of the patients ventilated for less than 5 days (57.1%) overall there is no statistical significance difference in days of mechanical ventilation regarding mortality. However, regarding VAP our study corroborate with the Egyptian study that has shown that increased number of ventilation days increases the chance of VAP.

Establishment of an artificial Airway in mechanical ventilation changes the mucosal defence, function of the normal Airway, ability of swallowing and scavenging capacity of the cilia and mucus is reduced. The bacteria can directly enter the lower respiratory tract or it can pass through a gap between the tracheal tube wall and the Airway which may lead to infection. Long term ventilation increases the risk of infection which can be caused by humidifiers and ventilator loop itself it can act as a source of pathogen due to exposure.

A Serbian study in 2015 have shown that the incidence of VAP patients with severe head injury was 49.7% which was much higher than the average incidence of VAP in our study also neurological diseases was the most common primary diagnosis in patients who have developed VAP. 31% in VAP, 61.9% in VAT and 44% in overall group. Musculoskeletal system and respiratory system when the next commonly involved system in patients who developed ventilator-associated infective complications.²² Probable causes may be that the protective reflexes in patients with neurological injury or disorder are weak. reflex is like cough, swallowing, expectorating are diminished in patients with neurological injury that hampers the clearance of respiratory secretions, also they have high chance of reflux of gastric content and aspiration.

In our study hypertension was the commonest comorbidity associated with VAP and VAT followed by diabetes incidence of comorbid conditions for more in patients with VAP than compared to patients with VAT however there was no statistically significant association of comorbidities with the outcome of the patients. These findings are similar to the findings seen in other studies like studies of But et al.¹³ Liu et al²¹ has shown that COPD can be independent risk factor for development of VAP all these medical conditions together leads to immunosuppression and increased vulnerability to infections that ultimately leads to VAIC (Ventilator

associated ineffective complication).

In our study 37% person patients were smoker in VAP group, in VAT group 14% patient were smokers, Liu et al²¹ in the study have found that there is a increase 4.37% increase in incidence of VAP in smoker patients than nonsmoker patients. Long term smoking impaired function of the pulmonary macrophages leading to decrease bacterial clearance resulting in an increased incidence of respiratory infections.

Although considered as an important risk factor in many studies regarding VAP and VAT²³ prior use of antibiotic was minimal in patient our study, also very minimal number of patients had history of previous Hospital admission in last 3 months. The finding of a study regarding most of the risk factors corroborates with other studies that has been done with ventilator-associated respiratory infection.

In our study 58% of the patients of VARI was VAP and 42% of VAT. At the same Centre U.Ray et al²⁴ have studied VAT and VAT patients in 2017 they included 212 patients admitted in ICU among which 28 patients develop VAT and 24 patients developed VAP. In their study incident of VAT was more compared to incident of VAP whereas in our study in 2020 in the same centre showed incident of VAP is more compared to incidence of VAT.

In our study we have studied relationship of SOFA score with severity of VAP and VAT in term of outcome. And SOFA in all the group was 6 in VAP it was 6.64 in VAT it was 6.68. Outcome wise the mean SOFA score was 8.19 ± 3.41 in death group and Discharge group was 5.68 ± 1.29 , this difference was statistically significant ($p=0.004$). Boeck et al also in their study have found similar results, in their study also mortality was higher in patients of VAP with a higher SOFA score.²⁵ Karakike et al²⁶ and Madan et al²⁷ have done similar observation in their study, in the first study they have studied the relationship of a higher SOFA score with mortality in patients with sepsis and in second study the mean SOFA score in surviving and non surviving group was studied, in both studies a high SOFA score was associated with poorer outcome.

We have also studied different modes of ventilator parameters and their association with the outcome of VAP and VAT. Mode of ventilation, tidal volume, respiratory rate, Fio₂, PEEP, Pressure support was studied but there was no statistical significance was found in relation to outcome.

We have a mostly studied endotracheal aspirates as a primary sample for diagnosis of VAT for VAT, bronchoalveolar lavage and tracheostomy tube aspirate was also sent for analysis in a group of patient.

In our study in overall group Klebsiella pneumoniae was the predominant organism along with Acinetobacter baumannii both had 40% incidence, other organisms include E coli (4%) Pseudomonas aeruginosa (6%) Providencia species (6%). VAP group Acinetobacter baumannii was the predominant organism (44.8%), followed by Klebsiella

pneumonia (37.9%), Other organism includes Providencia species (10.3%) and Pseudomonas aeruginosa(3.4%). In overall, VAP and VAT group only Gram Negative bacterium were isolated.

In VAT group Klebsiella pneumonia was the commonest organism (42.9%) followed by Acinetobacter baumannii (33.3%), other organism includes E coli(9.5%), Pseudomonas aeruginosa (9.5%), Enterobacter species (4.8%).

In the same centre study performed by U Ray et al in 2017(24) found that Acinetobacter baumannii was the commonest cause(40%) of VAT followed by Pseudomonas aeruginosa (40%) then Klebsiella pneumoniae(13%). In our study in 2021 we have found that Klebsiella pneumoniae is the commonest organism for VAT overtaking Acinetobacter and Pseudomonas. Ranjan et al²⁸ has also shown that the most common organism for VAP in their study was Acinetobacter baumannii followed by Pseudomonas aeruginosa. It was associated with higher mortality. In our study in VAP group Acinetobacter Baumanii was associated with 41% mortality and Klebsiella was also associated with 41% mortality. Overall mortality was high in VAP caused by these two organism. Although the mortality in VAT group was low, 50% of it was caused by Klebsiella pneumoniae (2 out of 4). The mean SOFA score in VAP patients with Acinetobacter baumannii was 6.73, for Klebsiella pneumoniae it was 6.69.

Overall sensitivity pattern that was observed in our study showed that about 80% isolates in overall group were intermediately sensitive to polymyxins. CLSI 2020 update has proposed that sensitivity reports will only mention intermediate sensitivity to polymyxin due to change in MIC cut off values.²⁹ The preclinical PK/PD, clinical PK/TD, and MIC distribution data indicate that an MIC value of 2 $\mu\text{g/mL}$ is the only viable clinical breakpoint for polymyxin however even with optimised drug regimen it is difficult to achieve a MIC breakpoint of 2 $\mu\text{g/mL}$ without clinical toxicity and lowering the breakpoint will make the MIC testing challenging. CLSI has reviewed the clinical data available, and they suggested that an intermediate only category was to be established because this category will identify isolate that approach usually attainable level blood and tissue and for which response rate may be lower than the susceptible isolates.³⁰ Other antibiotics that were used in our study were Tigecycline, Minocycline. aminoglycoside like Amikacin, Gentamicin, Cefoperazone+sulbactam, Cotrimoxazole. In VAP group also 79% of isolates were intermediate sensitive to Polymyxin, in VAT group about 80% of the isolates were intermediate sensitive to Polymyxin. Maebed et al³¹ study have also shown that most of the isolates were multidrug-resistant, out of date 28 isolates 6 isolates were pan drug resistant, in our study the number of pan drug resistant organism was low (only 1). Nseir et al¹⁰ in their study have

also used multiple classes of antibiotic similar to our study.

In our Study *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the predominant organisms. Out of twenty isolates of *Acinetobacter baumannii* all were intermediately sensitive for polymyxin. 11 were sensitive to Tigecycline, 5 were sensitive to Cefoperazone+sulbactam, 4 were sensitive to aminoglycosides, only one was sensitive to carbapenems. 20 Isolates of *Klebsiella pneumoniae* are there in our study, eighteen isolates were intermediately sensitive to polymyxin. For aminoglycoside and Tigecyclines 4 isolates were sensitive for each antibiotic, only two were sensitive to carbapenems. Cheema et al³² have shown that *klebsiella pneumoniae* was 100% resistant to Piperacillin tazobactam. *Acinetobacter* was 100% carbapenem resistant, in our study also carbapenem resistance was very high among these two organisms. Kahlil et al³³ study have found that *klebsiella pneumoniae* was 55% carbapenem sensitive. Carbapenems Sensitivity is very low in our study.

In our study 32% of the overall patients was blood culture positive, 44.8% patients of VAP were blood culture positive, in VAT 14.3% blood culture positive. Culture positivity rates were somewhat higher in our study, Luna et al³⁴ has shown only 6.9% blood culture positivity in patients of VAP. However, blood culture positivity has not affected the mortality, the mortality in among blood culture positive group and culture negative group is statistically non-significant. *Klebsiella pneumoniae* was the commonest organism that was isolated from the blood cultures in overall (10%), VAP(17.2%) group. The blood isolate of *Klebsiella pneumoniae* was intermediately sensitive to polymyxin.

Outcomes wise the mortality rate was higher in VAP group (58.6%) compared to VAT group (19%) which is statistically significant ($p=0.005$). Clinical variables age, sex, days of ventilation did not have any statistical significance regarding mortality. The difference of SOFA score among dead and discharged population was statistically significant ($p=0.004$). Other ventilatory parameters like respiratory rate, tidal volume, peak pressure, Fio2 did not have any statistically significant difference in dead and discharged population.

Ramírez-Estrada et al³⁵ study have shown that the 30 days mortality of VAP was much higher compared to mortality of VAT(42.8 vs. 19.6%, $p<0.007$). Our study also corroborates with these findings. In our study of the patients who died, 38.09% had infection with *Acinetobacter baumannii*, 42.85% had *Klebsiella pneumoniae* infection, 9% had infection with *Providencia* spp. Among patients who had *klebsiella pneumoniae* as their primary infection 44.4% had concomitant bloodstream infection by same or another organism. For *Acinetobacter baumannii* 50% of the isolates had secondary bloodstream infection. K. Ranjan et al²⁸ in their study have shown attributable mortality for VAP was 48.33%.

Acinetobacter and *pseudomonas* were the leading cause of VAP in their study also lead to higher mortality, in our study *Acinetobacter* and *Klebsiella* were the organisms responsible for higher mortality.

Čiginskienė et al³⁶ had found increased mortality with *Acinetobacter* VAP(63.3%), Although mortality in *Acinetobacter* VARI was also high in our study(38.09%), *Klebsiella pneumoniae* VARI was associated with highest mortality in our study(42.85%).

5. Conclusion

Our study was an observational study performed for the duration of one year. Our primary objective was to study the clinical microbiological risk factors for ventilator associated respiratory infection and its severity with the help of SOFA score. Our secondary objective was to find any correlation between these parameters and 28 day mortality of the patients. In our study we have found that ventilator-associated respiratory infections continue to be an important problem in ICU among which the incidence of VAP is more come back to VAT. Clinical parameters is an important risk factor with advancement of age risk increases, although difference in SOFA score in patients of VAP for VAT was not significant, higher SOFA score was associated with a higher mortality. *Klebsiella pneumoniae* and *Acinetobacter baumannii* remains the principal organism responsible for ventilator-associated respiratory infection, most of the strains are multidrug-resistant some were extensively drug-resistant. Most of the drug resistant strains remains intermediately sensitive to polymyxins, other options include Tigecycline, Minocycline, Aminoglycoside, and incidence of carbapenem resistance is high in our study. Blood culture positivity rate is also high in our ICU compared to similar studies in other ICUs. Outcome wise VAP was associated with higher mortality compared to VAT, In VAT group discharge rate was higher. Most of the mortality in VAP group was associated with drug resistant organism. From our data, we can conclude that we should be increasingly aware of ventilator-associated respiratory infections in ventilated patients. The risk of drug resistant organism is growing in day-to-day practice and polymyxins remains the drug to which most of the organisms are intermediately sensitive. Despite use of polymyxins in the mortality of VAP remains high.

6. Limitation of the Study

There are various limitations to our study. The sample size of our study was only 50 because of both time and Logistic constraints also due to the ongoing COVID-19 pandemic. Study with larger sample size might have addressed the issues better. Duration of our study was also limited to one year due to academic requirements. Similar study with larger duration could have been better. As our

study was only observational study we could not provide any recommendations for use of antibiotics in ventilator associated respiratory infection from our study, however we can make only suggestions for certain class of antibiotics depending on our local flora

7. Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; BAL: Broncho alveolar lavage; B-BAL: Bronchoscopic broncho alveolar lavage; CHF: Congestive heart failure; CLSI: Clinical laboratory standards institute; COPD: Chronic obstructive pulmonary disease; CPIS: Clinical Pulmonary Infection Score; CT: Computed tomography; CVA: Cerebro vascular accident; EA: Endotracheal aspirate; ET: Endotracheal tube; HTN: Hypertension; ICU: intensive care units; INICC: international nosocomial infection control consortium; MDR: Multidrug resistant; MV: mechanical ventilation; PMNL: Polymorphonuclear Leukocytes; PSB: Protected sample brushing; Q-FA: Quantitative culture; SOFA: Sequential organ failure Assessment; SQ: Semi quantitative; T2DM: Type 2 Diabetes Mellitus; VAIC: Ventilator associated infective complications; VARI: Ventilator associated respiratory infections; VAP: Ventilator-associated pneumonia; VAT: Ventilator-associated tracheobronchitis.

8. Source of Funding

None.

9. Conflict of Interest

None.

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