"ETIOLOGICAL FACTORS AND ANTIBIOTIC SENSITIVITY PATTERN OF VENTILATOR ASSOCIATED PNEUMONIA (VAP) IN ICU PATIENTS AT A TERTIARY CARE CENTRE, UTTAR PRADESH, INDIA".

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ABSTRACT

Introduction: The most common intensive care unit (ICU) acquired infection among patients receiving mechanical ventilation is ventilator-associated pneumonia (VAP). Accurate clinical and microbiological identification of VAP is crucial for both choosing the right antibiotics and avoiding antibiotic overuse. VAP is associated with prolonged duration of mechanical ventilation and ICU stay. The estimated attributable mortality of VAP is around 10%, with higher mortality rates in surgical ICU patients and in patients with mid-range severity scores at admission.

Methods: The present study was a prospective and descriptive study carried out in the Department of Microbiology and the ICU at a Tertiary care centre for a period of 2 years i.e, June 2021 to June 2023 . A total of 200 consecutive patients who were hospitalised in the ICU were included in the study. The patient's consent was duly taken and epidemiological clinical study was carried out. The OpenVAP was assessed in 200 patients who were mechanically ventilated and admitted to the ICU. To identify VAP, the Clinical Pulmonary Infection Score (CPIS) was employed and the microbiological profile was assessed. The organism was isolated and identified by the use of different biochemicals test followed by the Antimicrobial susceptibility testing by Kirby Bauer disc diffusion method following the CLSI guidelines 2021.

Results: In the present study 200 patients in the study cohort were included. Using the CPIS criteria >6 for the diagnosis of VAP, 48 (24%) developed VAP. The overall incidence among the ventilated patients during the given duration was 24% VAP rate per 100 patients. Of the 48 cases with VAP, 46 were Culture positive for organisms, however in two cases organisms were not isolated and VAP was diagnosed only based on CPIS score of more than six constituted

by the other variables. The most frequent organisms in our study were *Klebsiella pneumonia* (38.46%), *Acinetobacter calcoaceticus baumanni* (30.76%), *Acinetobacter wolfii* (11.53%) and *Pseudomonas aeruginosa* (9.61%) and *Escheresia coli* (9.61%). It was also observed that Colistin, Polymyxin B and Amikacin were the most sensitive antibiotics being sensitive in 83.3%, 65% , 64 % of the cases, respectively whereas the rate of sensitivity to Piperacillin Tazobactam was low.

Conclusion: Based on these findings, an empiric approach to antibiotic treatment can be developed and adapted for the particular circumstances. Antibiotic stewardship programmes must be widely implemented in all healthcare settings due to the severity of drug resistance and the associated economic and societal costs.

Keywords: VAP, ICU, Clinical Pulmonary Infection Score, Antibiotic stewardship programmes, CLSI.

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INTRODUCTION

The term "ventilator-associated pneumonia" (VAP) refers to pneumonia or an infection in the lung parenchyma that occurs in individuals 48 to 72 hours following invasive mechanical ventilation. Patients with VAP experience new or developing infiltrates, systemic infection (fever, altered white blood cell counts), changes in sputum characteristics, and the identification of a causal agent [1]. Among invasive mechanically ventilated patients, VAP is the most typical ICU acquired pneumonia [2]. VAP is acknowledged as a significant problem on a global scale, and prevalent healthcare-associated infections (HAI) in developing countries are linked to patient financial burden, longer lengths of stay, and mortality [3-5]. Variations in diagnostic criteria, ICU types, patient characteristics, and causative microorganisms linked to patient characteristics, length of stay, and antibiotic administration in hospitals all contribute to variation in the VAP rate among studies [6].

Oropharyngeal and gastric colonisation, thermal injuries, post-traumatic, postsurgical intervention factors like emergency intubation, reintubation, tracheostomy, bronchoscopy, and insertion of nasogastric tube, patients' body positioning, level of consciousness, stress ulcer prophylaxis, and use of medications like sedatives, immunosuppressive, and antibiotics are all VAP risk factors [7,8]. Despite significant advancements in microbiological instruments and the antimicrobials regimen for treatment, there is still some uncertainty regarding the epidemiology and diagnostic criteria for VAP. The patient's prognosis has deteriorated as a result of the delay in diagnosis and treatment with appropriate antibiotics, leads to the multi-drug resistant infections (MDR) [2,9].

The safety of patients can be increased and the frequency of adverse events can be decreased by improving infection-control procedures and surveillance systems [10,11]. Even after years of economic growth and development, the World Health Organisation (WHO SEAR) reports that the majority of nations in the South-East Asian region still have a high burden of infectious diseases [12].

Estimating the incidence, mortality, and etiological factors of VAP is the major goal of this study. This information would be useful for the clinicians, and policymakers for developing infection control and other preventive measures in addition to interventional educational programmes.

Therefore, the present study was undertaken to study the Microbiological profile, its risk factors and its adherence to Bundle care with association to the Antibiotic sensitivity pattern of ventilator associated Pneumonia (VAP) in ICU patients at a tertiary care centre in Uttar Pradesh.

MATERIAL AND METHODS

The present study was a prospective and descriptive study carried out in the Department of Microbiology and the ICU for a period of 2 year i.e, June 2021 to June 2023. A total of 280 consecutive patients who were hospitalised to the ICU were included in the study. The patient's consent was duly taken , where patient's demographic information, primary diagnosis, co-morbidities, and date of hospital and intensive care unit admission were recorded. A total of 280 patients hospitalised in a row enrolled with mechanically intubated were included in the study. Out of the 280 cases, 80 cases were disqualified because they had initially been diagnosed with pneumonia presentation, were diagnosed with ARDS upon admission, death of the patients within 48 hours or were moved from an ICU at another facility.

Each Patients in the trial were observed every third day, employing clinical and microbiological methods for the development of VAP until discharge or death, whichever comes first. Relevant information was recorded from radiography, bedside flow sheets, and medical records findings and reports on the patients' microbiological investigations

For the diagnosis of VAP, modified CPIS [3,4] criteria [Table 1] were applied. The first five variables—temperature, blood leukocyte count, tracheal secretions, oxygenation, and type of lung infiltrate—were used to evaluate CPIS at the baseline.

The calculation of CPIS at 72 h takes into account the development of the infiltrate, the results of the tracheal aspirate's culture, and all seven factors. At baseline or after 72 hours, a score of >6 was regarded as suggestive of ventilator-associated pneumonia.

In cases where VAP was suspected, the organisms that were cultured and their pattern of antibiotic sensitivity were reported. Using a sputum suction trap, the endotracheal aspirate (ETA) specimens were obtained.. The ETA samples were delivered to the lab in less than an hour and used right away for microscopic examination and semi-quantitative culture. The culture media employed were McConkey agar, Blood, and Chocolate agar.

The organism was cultured for 24 hours before being replated on Mueller Hilton agar to evaluate its resistance to antibiotics using the Kirby bauer Disc Diffusion method according to the CLSI guidelines 2021 [13]. Both the culture and antibiotic susceptibility test findings were read 48 hours later. Biochemical testing was used to perform additional organism typing. The microbiologist classified the growth as light, moderate, or heavy at his or her discretion.

RESULTS

Of the 200 patients in the study cohort, using CPIS criteria >6 for the diagnosis of VAP, 48 developed VAP. The VAP incidence was calculated as: Number of cases with VAP/ Total cases who received MV×100 = VAP rates per 100 patients.
Therefore, the VAP rate per 100 patients was 24%. All patients in the study were on emperical antibiotic treatment.

Time to the onset of VAP

The onset of VAP was more likely to occur during the first two weeks of Mechanical Ventilation as 81.25% (39 out of 48) occurred during this period. Early-onset VAP developed in 46% (22 out of 48) of the cases, while the rest were Late-onset VAP.

Microbiological study

Of the 48 cases with VAP, 46 were Culture positive for organisms, however in two cases organisms were not isolated and VAP was diagnosed only based on CPIS score of more than six constituted by the other variables. Of the 46 culture positive cases, in 40 cases single organisms were isolated and in six cases two organisms each were isolated, thus in total from 48 cases 52 organisms were isolated. The prevalence of isolated organisms is shown in [Table 2].
In the present study it was observed that the most frequent organisms in our study were *Klebsiella pneumonia* (38.46%) followed by *Acinetobacter calcoaceticus baumanni* (30.76%), *Acinetobacter wolfii* (11.53%), *Pseudomonas aeruginosa* (9.61%each) and *Escheresia coli* (9.61%).

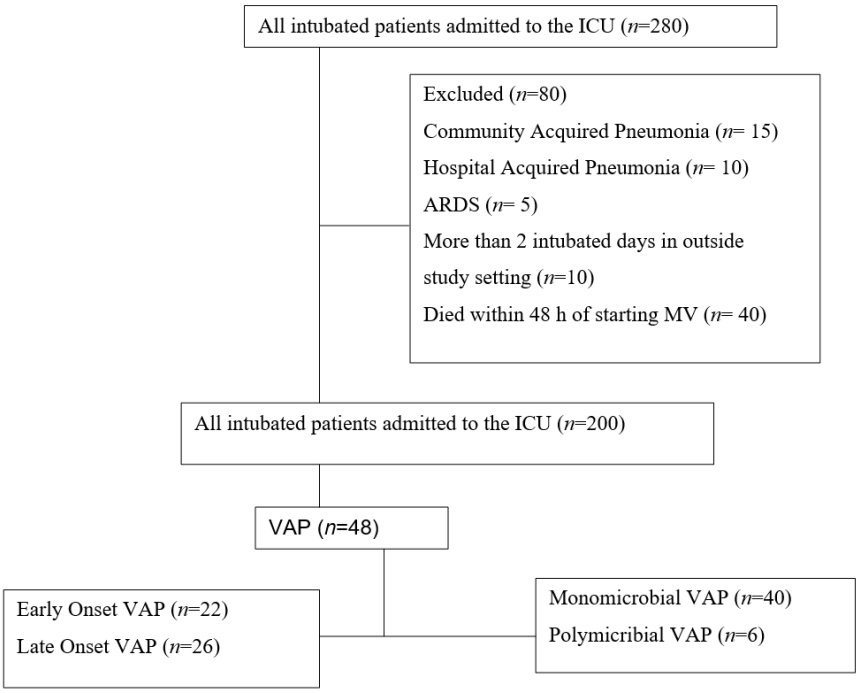


Figure No.1: Trial Profile of the patients

The Antibiotic sensitivity pattern

It was observed that the Colistin, Polymyxin B and Amikacin were the most sensitive antibiotics being sensitive in 83.3%, 65% , 64 % of the cases, respectively. The sensitivity of Imipenem and Meropenem were less than 50% of the time that they were tested. Cefepime and Ciprofloxacin were sensitive less than 5% of the time whereas the rate of sensitivity to Piperacillin Tazobactam was observed low [Table 3].

Susceptibility patterns of individual organisms

Klebsiella pneumonia

It was observed that among *Klebsiella pneumonia* (n = 20) isolates, 80% were susceptible to Amikacin. The susceptibility to Polymyxin B was 66.6 % and Colistin was found to be 50%. All other antibiotics had rates less than 50% for these isolates [Table 4].

Acinetobacter calcoaceticus baumanni

It was observed that *Acinetobacter calcoaceticus baumanni* (n = 16) isolates presented susceptibility rates of 100% for Colistin, 66.6% for Polymyxin B and 77% for Cefoperazone + Sulbactam. The susceptibility rates for Amikacin, Imipenem, Meropenem were all less than 60% [Table 4].

Pseudomonas aeruginosa

Among *Pseudomonas aeruginosa* (n = 5), the susceptibility to Colistin was 100% followed by Amikacin at 80% and Cefoperazone-Sulbactam at 75%. However, it was sensitive to Imipenem only 25% of the time as well as Piperacillin Tazobactum to 20% [Table 4].

Escheresia coli:

In the present study it was found that among *E. coli* isolates (n = 5), all were susceptible to Amikacin. However, the isolates were resistant in all cases to Meropenem, Polymyxin B, Colistin, Cefoperazone + Sulbactam [Table 4].

Acinetobacter wolfii

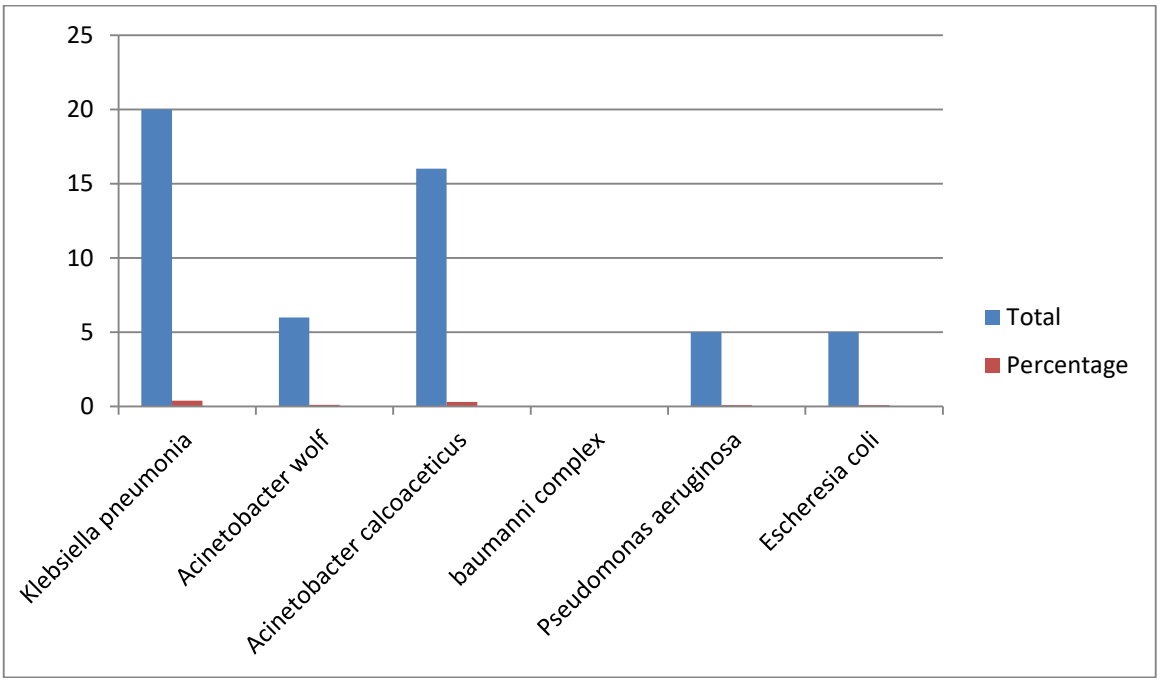
Acinetobacter wolfii (n = 6) presented susceptibility rates of 100% for Polymyxin B, and 50% for both Imipenem and Meropenem [Table 4].

Table No. 1: Modified CPIS Criteria

CPIS points	**0**	**1**	**2**
Temperature (T)	>=36.5 or <=38.4 >=97.7 or <=101.2	>= 38.5 or <= 38.9 >=101.3 or <=102.1	>=39 or <=36 >=102.2 or <=96.8
WBC count (W)	>=4000 or<=11,000	11,000	+band forms >=50%
Pao2/fio2 (O)	>240 or ARDS		<=240 and no ARDS
Tracheal secretions (S)	Absent	Non purulent	purulent
Chest x-ray (X	No infiltrate	Diffuse (or patchy) infiltrate	Localized infiltrate
Progression of	No radiographic progression		Radiographic progression (after
infiltrate (P.I.			CHF and ARDS excluded)
Culture of trachea	Pathogenic bacteria‡ cultured in rare or	Pathogenic bacteria cultured in moderate	Same pathogenic bacteria seen on
aspirate (C)	light quantity or no growth	or heavy quantity	Gram stain, add 1 point

Table No. 2: Prevalence of Isolated Organisms

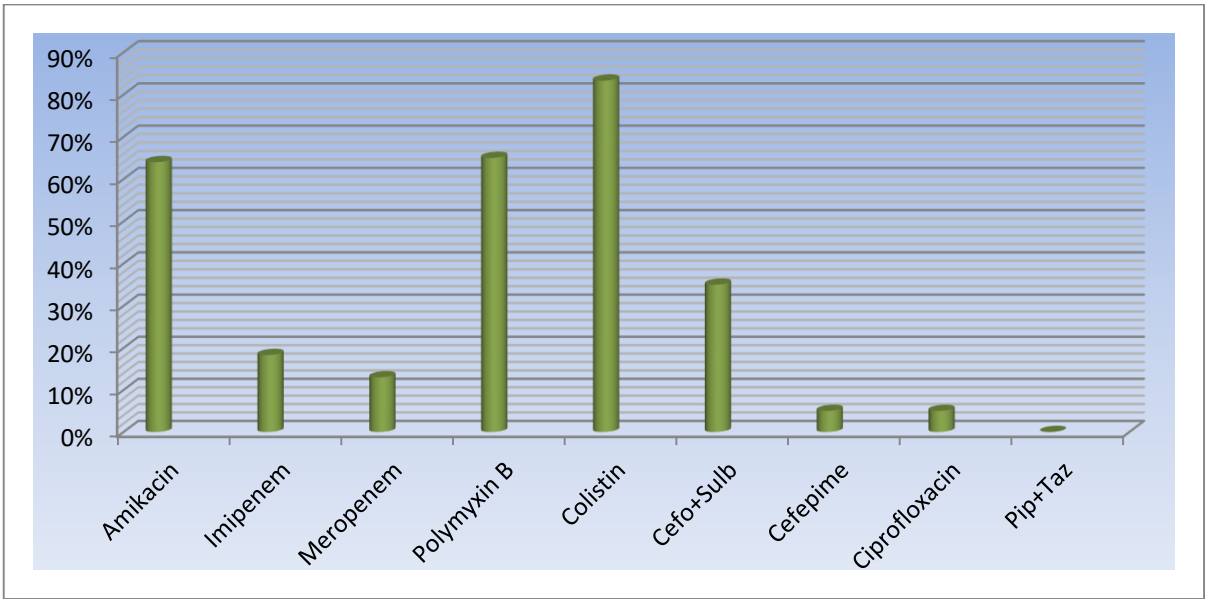
Organisms	**Monomicrobial**	**Polymicrobial**	**Total**	**Percentage**
Klebsiella pneumonia	14	6	**20**	**38.46%**
Acinetobacter wolf	4	2	**6**	**11.53%**
Acinetobacter calcoaceticus	12	4	**16**	**30.76%**
baumanni complex	-	-	-	-
Pseudomonas aeruginosa	2	3	**5**	**9.61%**
Escheresia coli	3	2	**5**	**9.61%**
Total	**35**	**17**	**52**	**100%**



Graph No. 1: The Graphical Representation of the Organisms Isolated

Table No. 3: Overall Antibiotic Sensitivity Pattern

Antibiotic	Sensitive (n/%)	Resistant (n/%)	Not tested	Percentage
Amikacin	30	17	5	64%
Imipenem	9	40	3	18.3%
Meropenem	6	40	6	13%
Polymyxin B	11	6	35	65%
Colistin	10	2	40	83.3%
Cefo + Sulb	8	15	29	35%
Cefepime	2	32	18	5%
Ciprofloxacin	2	44	8	5%
Pip + Taz	1	48	4	2%



Graph No. 2: The Graphical Representation of the Organisms Antibiotic Sensitivity Pattern

Table No. 4: Antibiotic Sensitivity Pattern of Isolated Organisms

***Klebsiella pneumonia* (n=20)**	***Acinetobacter calcoaceticus baumanni* (n=16)**	***Pseudomonas aeruginosa* (n=5)**	***Acinetobacter wolfii* (n=6)**	***E. coli* (n=5)**

	S	**R**	**Nd**	**S**	**R**	**Nd**	**S**	**R**	**Nd**	**S**	**R**	**Nd**	**S**	**R**	**Nd**
Amikacin	16 (80%)	4(20 %	-	2(16.66 %)	10 (83.33%)	4	4 (80%)	1 (20%)	_	1 (16.66 %)	5 (83.3 3%)	-	5(10 0%)	--	--
Imipenem	9 (47%)	10(52 .63%)	1	2 (16.6 6%)	10 (83.33%)	4	1 (20%)	4(80 %)	_	3(50%)	3 (50%)	-	2(40 %)	3(60 %)	--
Meropenem	8 (42.10 %)	11(57 .89%)	1	-	8(100%)	8	_	3 (100 %)	2	3(50%)	3(50 %)	-	--	5(100 %)	--
Polymyxin B	8(66.6 %)	4 (33%)	8	8 (66.6 6%)	4 (33.33%)	4	_	_	5	1(100 %)	__	5	--	4(100 %)	1
Colistin	2 (50%)	2 (50%)	16	8(100 %)	-	8	1 (100%)	_	4	__	__	6	--	4(100 %)	1
Cefoperazone + Sulbactam	1(6.66 %)	14 (93%)	5	7(77. 7%)	2 (22.22%)	7	3 (75%)	1 (25%)	1	__	5(100 %)	1	--	4(100 %)	1
Piperacillin Tazobactum	-	-	-	-	-	-	1(20%)	4(80 %)	-	-	-	-	-	-	-

DISCUSSION

VAP is one of the most significant intensive care unit (ICU) acquired infections in mechanically ventilated patients, and it poses a serious risk to their recovery. Depending on the demographic being investigated, there may be 100 patients with an increased risk of VAP due to underlying pulmonary illness [14]. The death rate for people developing VAP is 2.78 varies between 33 and 70% [15].

New or progressive infiltrates, systemic infection (fever, altered white blood cell counts), changes in sputum characteristics, and the detection of a causative agent are seen in VAP patients [16]. VAP is the most common ICU acquired pneumonia among invasive mechanically ventilated patients [17]. VAP is recognized as a major issue worldwide, and common healthcare-associated infection (HAI) among developing countries associated with mortality, longer length of stay, and associated cost burden among patients [18-20]. There is variability in the VAP rate in different studies caused by differing diagnostic criteria, ICUs type, patients' characteristics, and also varying causative microorganisms associated with patients' characteristics, length of stay and antibiotic use in hospitals [21].

In the present study of the 200 patients in the study cohort, using CPIS criteria >6 for the diagnosis of VAP, the overall incidence among the ventilated patients during the given duration was 48 (24%). The onset of VAP was more likely to occur during the first two weeks of Mechanical Ventilation as 81% (39 out of 48) occurred during this period. Early-onset VAP developed in 46% (22 out of 48) of the cases, while the rest were Late-onset VAP Of the 48 cases with VAP, 46 were culture positive for organisms, however in two cases organisms were not isolated and VAP was diagnosed only based on CPIS score of more than six constituted by the other variables. Of the 46 culture positive cases, in 40 cases single organisms were isolated and in six cases two organisms each were isolated, thus in total from 48 cases 52 organisms were isolated. This study was similar to the study performed by the Mishra D R et al., in 2020 where out of the 60 patients in the study cohort, using CPIS criteria >6 for the diagnosis of VAP, 25 (41.6%) developed VAP. The overall incidence among the ventilated

patients during the given duration was "26 VAPs per 1000 ventilator days" (25 of 976) [22].

Another study by Deebya R et al [22] stated that the onset of VAP was more likely to occur during the first two weeks of Mechanical Ventilation as 80% (20 out of 25) occurred during this period. Early-onset VAP developed in 44% (11 out of 25) of the cases, while the rest were Late-onset VAP. Stating that of the 25 cases with VAP, 23 were Culture positive for organisms, however in two cases organisms were not isolated and VAP was diagnosed only based on CPIS score of more than six constituted by the other variables. Of the 23 culture positive cases, in 17 cases single organisms were isolated and in six cases two organisms each were isolated, thus in total from 23 cases 29 organisms were isolated [22]. This finding was similar to the present study where the onset of VAP was more likely to occur during the first two weeks of Mechanical Ventilation as 81.25% (39 out of 48) occurred during this period. Early-onset VAP developed in 46% (22 out of 48) of the cases, while the rest were Late-onset VAP.

The most frequent organisms in the present study isolated were *Klebsiella pneumonia* (38.46%) followed by *Acinetobacter calcoaceticus baumanni* (30.76%), *Acinetobacter wolfii* (11.53%) ,*Pseudomonas aeruginosa* (9.61% each) and *Escheresia coli* (9.61%). This study was in accordance to the study conducted by the other investigator where the maximum number of isolates were of *Klebsiella pneumonia* and least for *E.coli* [22].

The data from 24 investigations conducted with ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed those results: Gram Negative Bacteria (GNB) represented 58% of recovered organisms [23]. The predominant gram negative bacteria were *P. aeruginosa* and *Acinetobacter s*pp., followed by *Proteus spp*., *Escherichia coli*, *Klebsiella spp*., and *H. influenza*. A relatively high rate of gram positive pneumonias was also reported in those studies, with *S. aureus* involved in 20% of the case [22], [24].

Interestingly, another study in India reports similar findings [25] whether the absence is due to a relatively small size of the sample or a trend actually exists will be an important consideration in further studies in our set up. In five cases suspected to have Active tuberculosis, appropriate stains and cultures were deployed however the results were negative.

In studies on endotracheal specimens, sensitivity ranged from 38 to 100% and specificity ranged from 14 to 100% [9]. The varied sensitivity perhaps reflects the lack of standardization of the procedure and varying parameters of comparison. Using CPIS for comparison, Khilnani *et al*. [25] had a sensitivity of 52% for Endotracheal specimens. Our study looked at the culture of aerobic bacterial organisms only since anaerobic and fungal cultures were not being routinely done in the study setting.

It is generally recognized that early onset VAP (within the first 4 days of hospitalization) in previously healthy patients not receiving antibiotics usually involves normal oropharyngeal flora, whereas late onset VAP (occurring after at least 5 days of hospitalization) and VAP in patients with risk factors for multidrug resistant (MDR) pathogens are more likely to be due to MDR pathogens [26].

However, in our study organisms did not differ in either early or late onset VAP. In both the groups, organisms isolated consisted of *K. pneumoniae, Acinetobacter spp., Pseudomonas aeruginosa and E. coli*. This might be due to the rampant use of antibiotics in many patients developing early onset VAP before their transfer to the ICU. Similar findings have been reported by Ibrahim et al [27].

In the current study there were 35 monomicrobial cases and 17 polymicrobial cases**.** This study was in support with the study by Combes *et al* [28] where 52% had monomicrobial infections and 48% had Polymicrobial infection were observed. In most studies the rate of Polymicrobial VAP ranges from 40 to 62% [29] In comparison, rate of Polymicrobial VAP was 26% among Culture Positive cases. It has been seen that antibiotic therapy prior to VAP onset seems to be associated with dramatically fewer polymicrobial infections,[28], this might be one of the reasons for our results given that prior antibiotics had been administered to all the patients. Microorganisms responsible for VAP may differ according to the population of patients in the ICU, the durations of hospital and ICU stays, and the specific diagnostic method (s) used.

In the present study it was observed that Colistin, Polymyxin B and Amikacin were the most sensitive antibiotics being sensitive in 83.3%, 65% , 64 % of the cases, respectively. The sensitivity of Imipenem and Meropenem were less than 50% of the time that they were tested. Cefepime and Ciprofloxacin were sensitive less than 5% of the time whereas Piperacillin Tazobactam was sensitive in 20% cases of *Pseudomonas aeruginosa*. This study was parallel to the study conducted by the other authors [22] [28].

In the present study it was observed that *Klebsiella pneumonia* (n = 20) isolates, 80% were susceptible to Amikacin. The susceptibility to Polymyxin B was 66% and Colistin 50%. This finding was similar to the study conducted by the other author [22].

Acinetobacter calcoaceticus baumanni (n = 16) isolates presented susceptibility rates of 100% for Colistin, 66.6% for Polymyxin B and 77% for Cefoperazone + Sulbactam. The susceptibility rates for Amikacin, Imipenem, Meropenem were all less than 50% . This study was similar to the study performed by the other author where *Acinetobacter calcoaceticus baumanni* showed of resistance to Amikacin (80%), Imipenem (83%) and most sensitive antibiotic was Polymyxin B, Colistin and Cefoperazone Sulbactam. Among *Pseudomonas aeruginosa* (n = 5), the susceptibility to Colistin was 100% followed by Amikacin at 80% and Cefoperazone Sulbactam at 75%. Similar results were observed where *Pseudomonas aeruginosa* was uniformly resistant in all cases to Meropenem, Cefepime and 80% to Piperacillin Tazobactam. The level of resistance to Ciprofloxacin and Imipenem were 75%. It was most sensitive to Colistin, Amikacin and Cefoperazone Sulbactam. This pattern reflects the intrinsic ability of *P. aeruginosa* to develop resistance to all known classes of antibiotics noted by American Thoracic Society, Infectious Diseases Society [16]. Among *E. coli* isolates (n = 5), all were susceptible to Amikacin. However, the isolates were resistant in all cases to Meropenem, Polymyxin B, Colistin, Cefoperazone + Sulbactam. Acinetobacter wolfii (n = 6) presented susceptibility rates of 100% for Polymyxin B, and 50% for both Imipenem and Meropenem. This study was parallel to the study by Mishra et al, 2020 [22].

In the ICU, antibiotic resistance is a serious issue. Most patients received broad spectrum antibiotics even in outpatient settings, particularly in underdeveloped nations. In our research, the antibiotic prescriptions were issued at the treating physician's discretion in lack of rules that are specific to our ICU setup. Amikacin, Polymyxin B, and Colistin were the most sensitive antibiotics. There was evidence of considerable opposition. fluoroquinolones, third-generation Cephalosporins, and even using Carbapenems. Contrary to popular belief, Piperacillin-Tazobactam used an empiric medication in our ICU up until this point and discovered to be resistant in most sample that was examined.

In the present study the rate of VAP was observed to be 24%. This finding was similar to the study by the other author Sharma A et al., 2020 where the incidence rate of vap was observed to be 19% [31]. A study by Neelima Ranjan et al., [32] recorded that Overall incidence of VAP to be 57.14% . This figure is at the higher end of the range of 15-58% as reported by other investigators [33]. Divergence of incidence can be attributed to several factors such as differences in the study population, differences in the definition of VAP, e.g. clinically versus microbiologically oriented and possibly, to the use of preventive strategies.

The higher prevalence of VAP in our study can be attributed to the fact that the total number of cases in the study and the study duration were less as compared to other studies showing lower incidence. One more reason for this high rate can be the lack of adequate nursing staff (nurse to patient ratio should ideally be 1:1 as compared to 1:4 in our institute) which may have adversely affected the quality of care given to patients. There is now a growing evidence that high work load and low staffing level increase the risk for negative patients outcomes such as death and healthcar-associated infections [30].

However, the diagnosis of VAP is often a problem. Accurate clinical and microbiologic diagnosis of VAP is essential for selection of appropriate antimicrobials and prevent emergence of multidrug resistant pathogens in the ICU [14]. As the organisms and their sensitivity pattern may differ in every ICU, the knowledge of the resident flora and their behaviour should be known for successful treatment.

CONCLUSION

VAP is one of the serious problem in the ICU leading to longer hospital stay higher treatment costs and increased mortality and morbidity. Prolonged mechanical ventilation is an important risk factor. In addition, prior use of antibiotics increases the risk of acquiring drug resistant pathogens. Therefore, the knowledge of the

important risk factors predisposing to VAP may prove to be useful in implementing simple and effective preventive measures including non-invasive ventilation, precaution during emergency intubation, minimizing a patient's stay on mechanical support and in an intensive care unit, avoidance of a supine position of patients, and minimize the use of histamine blockers and corticosteroids**.**

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