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CHARACTERIZATION OF PATHOGENS CAUSING VENTILATOR ASSOCIATED PNEUMONIA IN INTENSIVE CARE UNITS OF A TERTIARY CARE HOSPITAL – A PROSPECTIVE STUDY.

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) is the most common healthcare associated infection diagnosed in intensive care units (ICUs). It is caused mostly by potentially drug-resistant bacteria. **Aims and objectives:** The current study aimed at determining the bacteriological etiology of VAP and antimicrobial susceptibility pattern of the isolates causing VAP in the ICUs of our hospital. **Material and Methods:** A prospective study was carried out from January 2017 to December 2017 from ICUs of Regency hospital, Kanpur. A total of 135 lower respiratory tract samples (Endotracheal aspirate (ETA) and Transtracheal aspirate (TTA)) of patients on Mechanical ventilator (MV) suspicious of having VAP were received in Microbiology Department and processed. Organisms were isolated by standard microbiological techniques. The isolates were then subjected to identification and antimicrobial susceptibility testing using VITEK 2 – compact. **RESULTS:** The majority of bacterial isolates causing VAP were found to be Gram negative bacilli (95%). *Acinetobacter baumanii* accounted for 60.0% followed by *Klebsiella pneumoniae* 22.2%, *Pseudomonas aeruginosa* 8.9%. Other isolates were *Escherichia coli, Enterobacter cloacae* & *S. aureus*. Out of the 39 VAP cases, 17(43.6%) were categorized under early onset VAP (<96 hrs. on MV) and 22 (56.4%) under late onset VAP (>96 hrs. on MV). Polymicrobial growth was seen in 15.4% of VAP cases. Thirty-seven (82.2%) of the 45 VAP pathogens in our study were multi-drug resistant (MDR). **Conclusions**: Most of the pathogens causing VAP in our institute were multidrug resistant. Colistin and Tigecycline were found to be highly effective against multidrug resistant *Acinetobacter baumanii* and *Klebsiella pneumoniae*. The bacteriological approach for the management of VAP helps the clinicians in choosing the appropriate antibiotics.

KEYWORDS: Ventilator-associated pneumonia, Intensive care unit, Multi Drug resistant.

INTRODUCTION

VAP is defined as pneumonia that occurs 48 hours or more after endotracheal intubation or tracheostomy, caused by infectious agents not present or incubating at the time mechanical ventilation was started.[1] The chance of acquiring VAP increases by 1-3%/day of mechanical ventilation (MV). In India, occurrence of VAP among intensive care unit (ICU) patients varies from 9% to 24%. Global crude mortality rate of VAP ranges from 24% to 50%. [2] The chance of VAP occurrence and its prognosis is determined by various modifiable and non-modifiable factors which includes age & gender of the patient, severity of primary illness, intubation duration, number of re-intubation and host immune competence, presence of co-morbidities, multi-organ dysfunction, cranial trauma and coma.[2,3]

Based on the time of onset VAP is of two type, i.e., early onset ventilator associated pneumonia (EVAP) which occurs during the first 4 days of MV (<96 h) and late onset ventilator associated pneumonia (LVAP) , which develops 5 or more days after initiation of MV (>96 h). EVAP is mostly reported to be less severe and have a better prognosis than LVAP due to the association of LVAP with multidrug resistant pathogens leading to increased mortality and morbidity. The common pathogens causing VAP include aerobic gram negative rods such as, *Acinetobacter baumanii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli*.[4,5]

Early and appropriate antimicrobial therapy is an important goal in intensive care units dealing with life-

threatening infections. Data on the distributions of pathogens and drug-resistance patterns of causative organisms is crucial for optimal management. Surveillance of nosocomial infections like VAP in ICUs has received high level of attention and the outcome indicators are now used in benchmarking the quality of patient care. Therefore the aim of this study is to analyze the microbiological profile of VAP in our hospital, and prevalence of multi-drug resistant bacteria so as to reemphasize implementation of prevention strategies.

MATERIAL AND METHODS

A prospective study was carried out among patients admitted to ICU's of Regency hospital, a Tertiary Care Hospital in Kanpur during January 2017 to December 2017. A total of 2219 patients were admitted to the intensive care units during this period. Of these 622 (28%) patients were put on Mechanical Ventilation (MV). 135 (21.7%) patients on MV were clinically suspected to have developed VAP and were reviewed prospectively.

The diagnosis of VAP was based on clinical and microbiological criteria. A clinical suspicion of VAP was made in patients using Modified Clinical Pulmonary Infection Score (CPIS).[6] CPIS was developed by Pugin et al. using a combination of six clinical, radiologic, and microbiologic criteria: temperature, white cell count, sputum, oxygenation, culture of tracheal aspirates, and radiology;[7] each parameter was scored from 0 to 2 and a total score of >6 points suggested a diagnosis of VAP.[8,9]

A total of 135 lower respiratory tract samples (Endotracheal aspirate (ETA) and Transtracheal aspirate (TTA)) of suspected cases of VAP were received in Microbiology Department and processed. All samples were first vortexed for one minute followed by gram staining and culture. Gram stained smears showing >10 polymorphonuclear cells / low power field and ≥1 bacteria/ oil immersion field were considered significant.[9,10] Organisms were isolated by standard microbiological techniques following Semi-quantitative culture method using calibrated nichrome wire loop of 4mm that holds 0.01ml of solution. The media inoculated were 5% sheep blood agar (BA), MacConkey's agar (MA) Chocolate agar (CA) and Saboraud's dextrose agar (SDA) and incubated at 37° C under aerobic atmosphere. For diagnosis of VAP semi-quantitative culture threshold was considered as 10^5 cfu/ml. Any growth below the threshold was assumed to be due to colonization or contamination.[4,11-12] All significant cultures isolates were then subjected to identification and antimicrobial susceptibility testing using VITEK 2 – compact.

Inclusion criteria: Case group included patients of either sex, aged ≥ 18 years with mechanical ventilation, who developed pneumonia after 48 h of ventilation.

Exclusion criteria: Patients with pneumonia prior to mechanical ventilation and those developing pneumonia within 48 h were excluded from the study.

Patients on mechanical ventilation for less than 4 days (48-96 hours) were included in the early-onset VAP group and more than 96 hours were included in the late onset VAP group.

RESULT

A total number of 135 patients were included in this study, as they were on mechanical ventilator for more than 48 hours during the study period. 39 Out of 135 patients were diagnosed as VAP cases based on clinical and microbiological grounds. The incidence of VAP in our study was 28.89% and the VAP rate was 11.52 per 1,000 Ventilator days for the year 2017. 82% (32/39) cases were males. The occurrence of VAP was more common in the age group of 61-70 years (23.07%). [Fig. 1.]

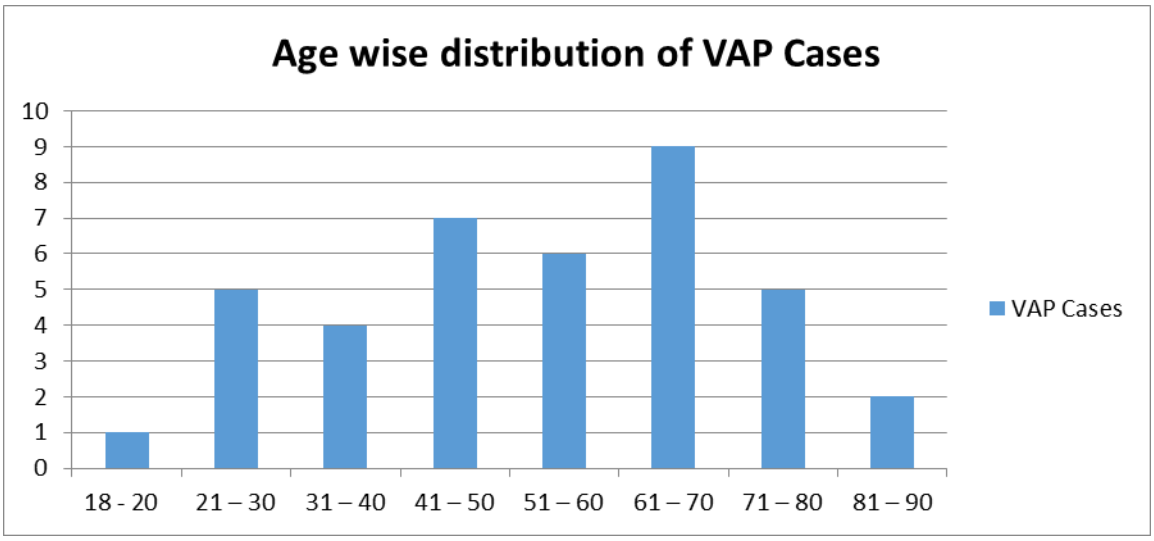

Fig. 1: Age wise distribution of VAP Cases.

Out of the 39 VAP cases, 17(43.6%) were categorized under early onset VAP (<96 hrs. on MV) and 22 (56.4%) under late onset VAP (>96 hrs. on MV) [Fig. 2.].

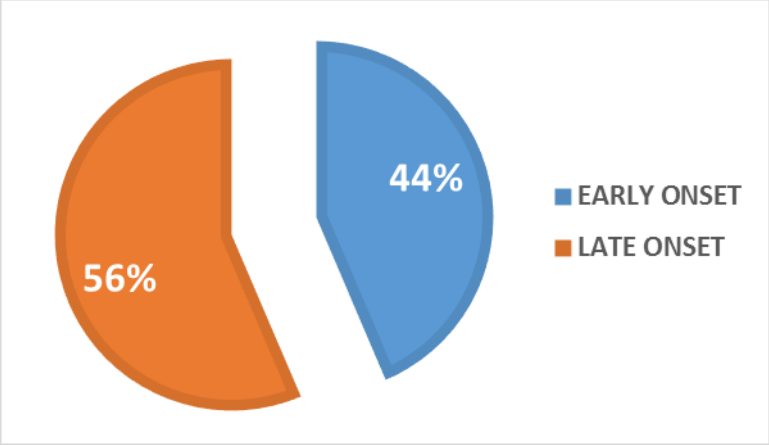

Fig. 2 : Distribution of Early and Late Onset VAP Cases.

Acinetobacter baumanii [27(60%)] is the commonest isolate causing both early and late onset pneumonia followed by *Klebsiella pneumoniae* [10 (22.2%)], *Pseudomonas aeruginosa* [4(8.9%)] and E.coli [2(4.4%)]. One isolate of *Enterobacter cloacae* and one isolate of *Staphylococcus aureus* was isolated from early and late onset VAP respectively [Table 1].

Table 1: Distribution of organism in Early & Late VAP.

S.no.	Bacterial isolates	Early onset	Late onset	Total
1.	*Acinetobacter baumannii*	10 (58.8)	17 (60.7)	27 (60.0)
2.	*Klebsiella pneumoniae*	3(17.6)	7 (25)	10 (22.2)
3.	*Escherichia coli*	1(5.9)	1 (3.6)	2 (4.4)
4.	*Enterobacter cloacae*	1(5.9)	0	1 (2.2)
5.	*Pseudomonas aeruginosa*	2(11.8)	2 (7.1)	4 (8.9)
6.	*Staphylococcus aureus*	0	1 (3.6)	1 (2.2)
	Total	17(37.8)	28 (62.2)	45 (100)

Among the 39 VAP cases, 33(84.6%) were monomicrobial and 6 (15.4%) were polymicrobial, thus yielding 45 isolates. 4 polymicrobial cases had a combination of *Acintobacter baumanii* and *Klebsiella pneumoniae* infection. A case each of *Acintobacter baumanii* with *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* with *pseudomonas aeruginosa* was seen.

All the 27 (100%) isolates of *Acinetobacter baumannii* were multidrug resistant (MDR) i.e. resistant to three or more class of antibiotics. Among the 27 isolates of *Acinetobacter baumannii*, maximum were susceptible to Colistin (96.3%) followed by Tigecycline (66.7%). 1(3.7%) was resistant to all antibiotics tested in this study including Tigecycline and Colistin (Pan drug resistance). 4 isolates of *Klebsiella pneumoniae* were susceptible only to Colistin and 3 were susceptible to Tigecycline and Colistin, one isolate had pan resistance towards all antibiotics tested. *E.coli* isolates were 100% susceptible to tested Carbapenems, Aminoglycosides and Tigecycline, Colistin. *Pseudomonas aeruginosa* isolates were 75% susceptible to most of the antibiotics tested, and 100% susceptible to Colistin. *Enterobacter cloacae* isolate was susceptible to Cefoperazone sulbactum, Carbapenems, Amikacin and Colistin. [Table: 2] The isolate of *Staphylococcus aureus* was MRSA susceptible only to Tigecycline, Linezolid and Vancomycin. [Table: 3].

Table 2: Antibiotic susceptibility pattern of Gram Negative bacteria isolated from VAP patients (% susceptible).

Bacterial isolate	No. of isolate	Ampicillin Sulbactum	Piperacillin Tazobactum	Ceftriaxone	Cefoperazone Sulbactum	Cefipime	Imipenem	Meropenem	Levofloxacin	Gentamycin	Amikacin	Cotrimoxazole	Tigecycline	Colistin
Acinetobacter baumannii	27	1 (3.7)	0	0	4 (14.8)	0	1 (3.7)	0	0	0	0	1 (3.7)	18 (66.7)	26 (96.3)
Klebsiella pneumoniae	10	0	0	0	0	0	2 (20)	1 (10)	0	1 (10)	1 (10)	1 (10)	5 (50)	9 (90)
Escherichia coli	2	0	1 (50)	0	0	0	2 (100)	2 (100)	0	2 (100)	2 (100)	1 (50)	2 (100)	2 (100)
Enterobacter cloacae	1	0	0	0	1 (100)	0	1 (100)	1 (100)	0	0	1 (100)	0	0	1 (100)
Pseudomonas aeruginosa	4	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	---	4 (100)

Table: 3 Antibiotic susceptibility pattern of Gram Positive bacteria isolated from VAP patients (% susceptible).

Bacterial isolate	No. of isolate	Ampicillin Sulbactum	Cefuroxim	Ciprofloxacin	Levofloxacin	Erythromycin	Clindamycin	Doxycyclin	Tigecycline	Gentamycin	Linezolid	Vancomycin	Teicoplanin
Staphylococcus aureus	1	0	0	0	0	0	0	0	1 (100)	0	1 (100)	1 (100)	1 (100)

DISCUSSION

Hospital‑acquired infections (HAIs) are a serious threat to global public health and one of the primary causes of patient morbidity and mortality & VAP is the most frequent ICU acquired HAI. The rate of VAP in our study was 11.52 /1000 ventilator days. Data from NHSN US suggest a pooled mean VAP rate of 2.04 per 1,000 & INICC India pooled mean VAP rates of 9.4 per 1000 ventilator days.[13] The VAP rate of our ICU's is much higher to pooled mean VAP rates given by NHSN US and comparable to INICC India pooled mean VAP rates.

Our study shows that patients in the age group of 40-70 years were more prone to VAP as the number of patients exposed to mechanical ventilation (>48hours) were also more in this age group. This was found in accordance with study by Girish N et al. , while a study by Ravi et al. showed higher infection rate in age group 21-40 years.[3,14] The incidence of VAP was more in males 82% (32/39) compared to females, which was similar to study conducted by Shiva et al.[15]

LVAP amounted to a larger percentage (56.4%) of all VAP cases in our study which is in accordance with several studies like Torres et al., Ravi et al., Khelgi et al.[3,10,16] Fagon et al. estimated an increased risk of 1% per day of mechanical ventilation.[17] Similar Bacteria were identified in both early and late VAP in our study, same finding was present in study by Khelgi et al and Ravi et al.[3,10] The American thoracic society guidelines for VAP states that EVAP is generally caused by less virulent organisms such as methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumonia*, in contrast our study has shown higher prevalence of virulent organisms even with EVAP.[18] The changing microbial pattern with a shift toward more gram negative pathogens in EVAP is very evident. There were no cases of *S. pneumonia* and *H. influenzae* in the present study. Though similar isolates were seen in early and late VAP but the percentage of their isolation was variable in a study by Girish N et al. whereas in our study isolates of MDR *Acintobacter baumanii* and *K. pneumoniae* had nearly similar percentage of isolation both in early and late VAP cases.[14] Being a tertiary care hospital nearly 40 - 50% of our patients were referred from another ICU after a prolonged and complicated course, very often post intubation, thus the patients of EVAP in our study were exposed to risk factors for MDR pathogens, especially prior antibiotics.

In our hospital setting, Gram negative organisms were predominant pathogens isolated from VAP patients, the most common organism being *Acintobacter baumanii*, which was isolated from 27 patients (60%),followed by *Klebsiella pneumoniae* in 10 (22.2%), *Pseudomonas*

aeruginosa in 4 (8.9%), *E.coli* in 2 (4.4%), and *E. cloacae* in 1(2.2%) of VAP cases. In a study conducted by Trouillet J. L. et al, *Staphylococcus aureus* (21.3%) was the most frequent organism isolated from VAP cases followed by Enterobacteriaceae (17.9%) and *Pseudomonas aeruginosa* (15.9%).[19] A study by Ranjan et al, Shiva et al also reported *Acintobacter baumanii* to be the most commonly isolated organism followed by *P.aeruginosa, K.pneumoniae, and E. cloacae*.[1,15]

Thirty-seven (82.2%) of the 45 VAP pathogens in our study were multi-drug resistant (MDR). Such high percentage of MDR is seen in study by Saravu K et al. and Joseph NM et al.[2,4] *Acinetobacter baumanii* was 60% (27/45) including one case of pan drug resistance, which is similar to a previous study.[2,5,20] Ranjan et al. and Rakshit et al. had 29% and 21.4% prevalence of *Klebsiella pneumoniae* and our study showed 22.2 % isolates with most of them being MDR.[1,20] The only identified *S. aureus* in LVAP was MRSA, many studies had shown high prevalence of MRSA cases.[2,14] Polymicrobial infection was seen in 15.4% (6/39) cases of VAP in our study. Various studies shows prevalence of polymicrobial infection in the range of 5% to 50%.[3,5]

CONCLUSION

An early, appropriate, empirical antibiotic therapy depending on the likely pathogens followed by de-escalation depending on the microbiological culture results and clinical response of patients is a key for management of VAP. The prevalence of causative organisms responsible for VAP varies with different healthcare settings. Most of these organisms, especially isolated from patients in tertiary care hospitals are multi-drug resistant MDR organisms especially *Acinetobacter*, *Klebsiella* and *Pseudomonas* are associated with majority of VAP cases. Knowledge of these prevalent organisms in the given healthcare facility (e.g. Gram negative organisms in our study) is useful to formulate an effective empirical antibiotic policy for patients who may be at risk of developing VAP, which will also reduce their hospital stay and cost of the treatment.

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