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RESEARCH ARTICLE

STUDY OF VENTILATOR ASSOCIATED PNEUMONIA IN TERTIARY CARE HOSPITAL, CENTRAL VIDARBHA

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ABSTRACT

Introduction: Ventilator associated pneumonia (VAP) is a type of nosocomial pneumonia which occurs in patients who receive 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%.

Aims and objectives: To determine the incidence rate, bacteriological profile and antibiotic sensitivity pattern of VAP. To determine Multidrug resistance pattern among the isolates.

Materials and methods: 245 ICU infected patients who were on MV > 48 hours were studied prospectively in the Department of Microbiology, Indira Gandhi Govt. Medical College from Sep. 2010- Dec. 2012. After the clinical confirmation according to CDC criteria, the endotracheal secretion were collected and processed as per standard microbiological methods and antibiotic sensitivity pattern of each were recorded. ESBL, AMPC, MBL along with MRSA were detected.

Results: Of total 107 clinically and microbiological diagnosed VAP patient, 114 isolates were obtained. Most common Organism isolated are *Pseudomonas aeruginosa* (33.6%), *Acinetobactor spp*. (29.9%), *Klebsiella pneumoniae* (26.2%) and Gram positive coccii (8.4%). Maximum gram negative isolates were sensitive to imipenem followed by piperacillin-tazobactum and amikacin. All *Staphylococcus* and *Enterococcus* species were sensitive to vancomycin and linezolid. High MDR were obtained.

Conclusion: Due to the increasing incidence of multidrug-resistant organisms in our ICU, early and correct diagnosis of VAP is an urgent challenge for an optimal antibiotic treatment and cure. Hence, knowing the local microbial flora causing VAP and effective infection control practices are essential to improve clinical outcomes.

INTRODUCTION

Ventilator associated pneumonia (VAP) is a type of nosocomial pneumonia which occurs in patients who receive mechanical ventilation (MV) via tracheal or tracheostomy tube (Charle *et al*., 2013). VAP refers to the development of parenchymal lung infection after a patient has undergone intubation and received MV for ≥ 48 hours (Coppadoro *et al*., 2012). 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%. In VAP due to highly resistant organisms, the crude mortality can be as high as 76 % (Coppadoro *et al*., 2012; Strausbaugh, 2000; Rakshit *et al*., 2005; Joseph *et al*., 2010; Chastre and Fagon, 2001; Kucukates, 2005). The main route for acquiring VAP is gross or micro aspiration of oropharyngeal organisms into the distal bronchi, either directly or secondarily by reflux from the stomach into the oropharynx.

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Other potential routes are less common, such as haematogenous carriage of microorganisms to the lung from remote sites of local infection (eg, catheter-related bloodstream infections or from the environment, especially from the hands of health care workers) or contaminated respiratory equipment, bronchoscopes, medical aerosols, water or air (Golia *et al*., 2013). American Thoracic Society subdivides VAP into early onset (within the first 4 days of the hospitalization) and late onset (usually occurring after the 5th hospital day) (American thoracic society and the infectious diseses society of America, 2005). Early onset nosocomial pneumonia tends to carry a better prognosis, whereas late onset nosocomial pneumonia tends to be associated with multidrug resistant (MDR) organisms, means it is associated with high mortality rates. VAP requires a rapid diagnosis and initiation of appropriate antibiotic treatment, as there is adverse effect of inadequate antibiotic treatment on patient's prognosis and the emergence of MDR pathogen (Golia *et al*., 2013). Inadequate antimicrobial therapy, such as inappropriate antimicrobial coverage, or delayed initiation of antimicrobials has been associated with higher hospital mortality in subjects with

hospital acquired pneumonia or VAP (Strausbaugh, 2000; Golia *et al*., 2013). Appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents to cover the MDR pathogens. Thus this study was conducted to determine the incidence rate, bacteriological profile and antibiotic sensitivity pattern of VAP in intensive care unit (ICU).

MATERIALS AND METHODS

The study was carried out in Department of Microbiology at a tertiary care institute, Indira Gandhi Government Medical College Nagpur, from September 2009 to December 2011.
All patients admitted in the ICU who received MV were included in the study. Patients who were on MV for less than 48 hours and those who had developed pneumonia prior to initiation of MV were excluded from the study. The study was approved by the institute ethics committee. Informed consent was obtained from the patient's next of kin.

Microbiological methods

Endotrachal tube (ET) aspirates were collected under aseptic precaution. ET aspirates was serially diluted in sterile normal saline as 1/10, 1/100, 1/1000 and 0.01 ml of 1/1000 dilution was inoculated on 5% sheep blood agar, chocolate agar, MacConkey agar by using 4 mm Nichrome wire loop (Hi-Media, Mumbai, India). After incubation at 37°C in 5% CO_2 incubator for 24 hours, colony count was expressed as number of colony forming units per ml (CFU/ml). The number of CFU/ ml is equal to number of colonies on agar plate ·dilution factor · inoculation factor. Therefore, the presence of a single colony on the blood agar after inoculating 0.01 ml of 1/ 1000 times diluted EA was interpreted as more than 10^5CFU/ ml (Nagendra *et al*., 2001; Payal *et al*., 2012). VAP was diagnosed in patients who fulfilled both clinical and microbiological criteria. A clinical diagnosis was made with the use of the Modified Clinical Pulmonary Infection Score (CPIS) based on six clinical assessments, each worth zero to two points (Strausbaugh, 2000).

VAP was confirmed microbiologically in patients with quantitative endotracheal aspirate culture indicative of $\geq 10^5$ CFU/ml with a positive Gram stain (>10 Polymorphonuclear cells/ high power field and ≥ 1 bacteria/ oil immersion field). The isolates were identified based on standard bacteriological techniques (Collee *et al*., 1996). A detailed biochemical testing identified any significant growth and antibiotic sensitivity testing was performed on Mueller–Hinton agar plates by Kirby—Bauer disc diffusion method. Zone diameter was measured and interpreted as per the Clinical and Laboratory Standards Institute (CLSI-2011) guidelines (Clinical and Laboratory Standards Institute, 2011). Suspected extended-spectrum beta lactamases (ESBLs) producing organisms were confirmed by CLSI phenotypic confirmatory test (Clinical and Laboratory Standards Institute, 2011). Detection of plasmid-mediated AmpC was done by the AmpC disk test and the isolates showing reduced susceptibility to carbapenems (imipenem and meropenem) were selected for detection of metallo-beta lactamases (MBLs) enzymes by imipenem-EDTA disk method (Clinical and Laboratory Standards Institute, 2011). For quality control of disc diffusion tests ATCC control strains of *Escerichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27853 strains were used (Clinical and Laboratory Standards Institute, 2011).

Table 1. Clinical Pulmonary Infection Score (CPIS) for diagnosis of nosocomial pneumonia[3]

Sr no.	Criterion	Values	Score
1	Temperature^{0}C	> 36.5 and < 38.4	0
		38.5 and < 38.9	1
		> 39 and < 36	2
2	Blood leukocyte/µl	>4000 and < 11,000	0
		< 4000 or >11,000	1
		Band forms > 500	2
3	Tracheal secretions	Absence of tracheal secretions	0
		Presence of nonpurulent tracheal secretions	1
		Presence of purulent tracheal secretions	2
4	Oxygenation, Pao_2/FiO_2 mmHg	> 240 or ARDS	0
		< 240 and no evidence of ARDS	2
5	Pulmonary radiography	No infiltrate	0
		Diffused(or patchy) infiltrate	1
		Localized infiltrate	2
6	Progression of pulmonary infiltrate	No radiographic progression	0
		Radiographic progression (after CHF & ARDS excluded)	2
7	Culture and Gram stain of tracheal aspirate	No pathogenic bacteria cultured	0
		Pathogenic bacteria cultured	1
		Some pathogenic bacteria seen on Gram stain	1

(ARDS, adult respiratory distress syndrome; CHF congestive heart failure; Pao2/FiO2, ratio of arterial oxygen pressure to fraction of inspired oxygen)

RESULTS

A total number of 245 patients were included in this study, as they were on mechanical ventilator for more than 48 hours during the study period. Out of 245, only 107 patients were diagnosed as VAP cases based on clinical and microbiological diagnosis criteria. The incidence of VAP in present study was 43.7%.

Table 2. General characteristics of 245 mechanically ventilated patients

Type of intensive care unit, n (%)	
Surgical	- 29 (27.1%)
Medical	- 78(72.9%)
Age, median (IQR)	- 48 (51-60)
Gender (female/male)	- 37/70
Previous use of antibiotics, n	- 88 (%)
Early onset VAP < 4 days	- 60 (56.1)
Early onset VAP > 4 days	- 47 (43.9)
Co morbidities, n (%)	
Immunosuppressive state	- 12 (11.2%)
Chronic renal failure	- 6 (5.6%)
Chronic obstructive pulmonary disease	-30 (28.0%)
Diabetes	- 20 (18.7%)
Alcoholism	- 6 (5.6%)
Cancer	- 3 (2.8%)
Chronic heart failure	- 6 (5.6%)
Organaphosphorus poisoning	-24 (22.4%)

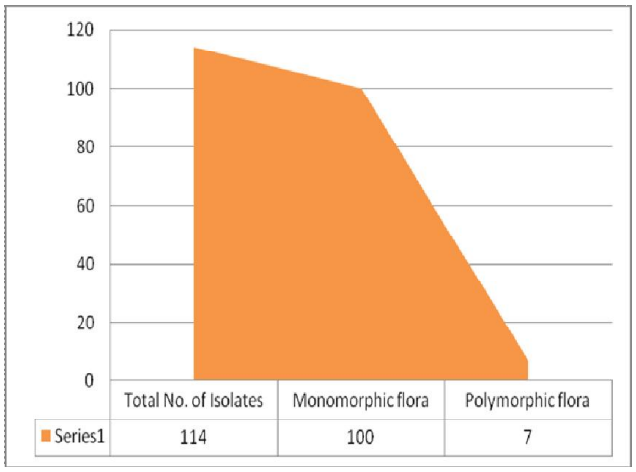

Fig. 1. Distribution of monomorphic and polymorphic flora of 107 VAP patients

Table 3. Bacterial aetiology in VAP cases

Isolates	VAP (n=114)
E. coli	8 (7.5%)
K. pneumoniae	26 (26.2%)
C. freundii	2 (1.9%)
E. cloacae	1 (0.9%)
P. aeruginosa	36 (33.6%)
A. baumannii	32 (29.9%)
S. aureus	9 (8.4%)

Table 3 shows, 33.6% *P. aeruginosa* was commonest aetiological agent in VAP followed by 29.9% *A. baumannii* and 26.2% *K. pneumoniae* isolates.

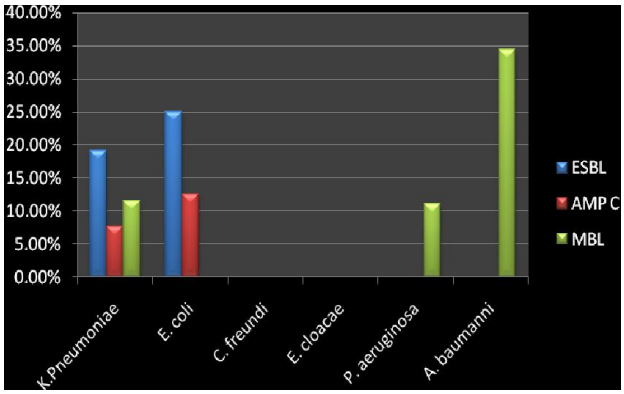

Fig. 2. β- lactamase profile of Gram negative bacilli in VAP

Table 5. Antimicrobial sensitivity of gram positive cocci (n= 7)

Drugs	*S. aureus* n=7 (%)
Penicillin G	0
Cefoxitin	4(44.4)
Erythromycin	0
Gentamicin	7(77.7)
Amikacin	7(77.7)
Tobramycin	2(22.2)
Netillin	1(11.1)
Rifampicin	3(33.3)
Ciprofloxacin	3(33.3)
Vancomycin	9(100.0)
Linezolid	9(100.0)
Chloramphenicol	3 (33.3)
Tetracycline	2 (22.2)
Cotrimoxazole	3 (33.3)
Clindamycin	2 (22.2)

Table 4. Antimicrobial sensitivity of Gram Negative Bacilli (n=105)

Drugs	*K. pneumoniae* n= 26(%)	*E. coli* n=8 (%)	*C. freundii* n=2 (%)	*E. cloacae* n=1 (%)	*A.baumanni* n=32(%)	*P. aeruginosa* n=36 (%)	Total(n=105)
Ampicillin	0	0	0	0	-	-	0
Amoxyclav	0	0	0	0	-	-	0
Cephalothin	0	0	0	0	-	-	0
Cefuroxime	1 (3.8)	1 (12.5)	0	0	-	-	2(1.9)
Ceftazidime	4 (15.4)	1(12.5)	0	1(100)	3 (9.4)	15 (41.7)	24(22.9)
Cefotaxime	4 (15.4)	1 (12.5)	0	0	2 (6.3)	10 (27.8)	17(16.2)
Cefipime	8 (30.7)	4 (50.0)	2 (100.0)	1 (100)	4 (12.5)	14 (38.9)	33(31.4)
Piperacillin	10 (38.5)	0	1 (50.0)	1(100.0)	6 (18.8)	14 (38.9)	32(30.5)
Piperacillin + tazobactum	14 (53.8)	3 (37.5)	2(100.0)	1(100.0)	19 (59.4)	31 (86.1)	70(66.7)
Imipenem	21 (80.8)	8 (100)	2(100.0)	1(100.0)	20 (62.5)	32 (88.9)	84(80.0)
Gentamicin	9 (34.6)	6 (75)	1 (50.0)	1(100.0)	7 (21.9)	17 (47.2)	41(39.0)
Amikacin	12 (46.2)	6 (75)	1 (50.0)	1(100.0)	15 (46.9)	24 (66.7)	59(56.2)
Tobramycin	4 (15.4)	3 (37.5)	2(100.0)	0	9 (28.1)	10 (27.8)	28(26.7)
Ciprofloxacin	8 (30.7)	1 (12.5)	1 (50.0)	1(100.0)	8 (25)	13 (36.1)	32(30.5)

Table 4 shows that maximum gram negative bacilli were sensitive to imipenem (80.0%) followed by piperacillin -tazobactum (66.7%), amikacin (56.2%), and gentamicin (39.0%), All isolates were resistant to ampicillin, amoxyclav, 1st generation cephalosporins.

Table 5. shows that all gram positive cocci were 100% sensitive to linezolid and vancomycin. Four (44.4%) isolates of *S. aureus* were found to be sensitive to cefoxitin. 5 (55.5%) isolates of *S. aureus* were found to methicillin resistant by cefoxitin disc diffusion method.

DISCUSSION

VAP is a leading cause of morbidity and mortality in ICU patients, leading to lengthened ICU and hospital stays and higher health care costs (Golia *et al*., 2013). VAP continues to be an important challenge to the critical care physician and is the most common nosocomial infection among patients with acute respiratory failure. It is difficult to diagnose accurately, and a high index of suspicion is required. The mortality caused by VAP increases if it is caused by resistant bacteria (Payal *et al*., 2012). The incidence of VAP in our study was 43.7%, which was similar to studies done by Dey *et al*. (2007) (45.4%).Woske *et al*. (2001) and Jamaati *et al*. (2010) reported 40.4% and 48% VAP cases respectively in their studies. Lower incidence rates were reported by Yehia *et al*. (2008) (33%). Mukhopadhyay *et al*. (2003) who reported a very high incidence rate of VAP (81.7%). Our study shows that patients in the age group of 51-60 years were more prone to VAP as the number of patients exposed to mechanical ventilation (>48hours) were also more in this age group and this was found in accordance with earlier studies (Golia *et al*., 2013). The incidence of VAP was more in males (65.4%) compared to females (34.6%) which was similar to studies conducted by Sharma *et al*. Out of 107 VAP cases, 60 (56.1%) were categorized under early-onset VAP and 47 (43.9%) under late-onset VAP which was in concordance with studies conducted by Saravu *et al*. (2013). Rates of polymicrobial infection vary widely. In our study only 6.5% of cultures were polymicrobial. In a study by Modi *et al*., 7.0% isolates were polymicrobial (Dey *et al*., 2007). Other studies have reported even higher rates (Golia *et al*., 2013).

In this study (33.6%) *Pseudomonas aeruginosa*, (29.9%) *Acinetobacter baumanni* followed by 26.2% *K. pneumoniae* were the commonest isolates obtained in VAP cases, which were also reported as the commonest isolates by other studies (Payal *et al*., 2012; Dey *et al*., 2007; Woske *et al*., 2001). Few studies have shown gram positive cocci mainly *Staphylococcus aureus* as the most frequently isolated organism in VAP which is in contrast to our study (Woske *et al*., 2001). Golia *et al*. (2013) and co-workers also reported gram negative bacilli as the commonest etiological agents of late onset VAP which remains the same in our study also. In our study, 27.1 % *Enterobacteriaceae isolates* were ESBL producers. Kucukates *et al*., also observed 21.1% ESBL prevalence rates in their study (Kucukates, 2005) while few studies shown higher ESBL rates (Singhal et al., 2005). In this study, we observed 8.1% AmpC β-lactamase producers in enterobacteriacae isolates. Singhal *et al*. (2005) also reported similar rates of AmpC production. Imipenem resistance was high in this study. Out of 21 Imipenem resistant isolates, 18 isolates were confirmed as MBL by imipenem-EDTA disk method. 17.1% gram negative bacilli were MBL producers were noted in our study. 34.4% of Acinetobacter species, 11.1% of the Pseudomonas and 11.5% Klebsiella isolates showed MDR, even to carbapenems, which is in concordance with other studies (Golia *et al*., 2013; Navneeth *et al*., 2002). Whereas certain studies reported higher incidence of meropenem resistance (Wattal *et al*., 2010; Gopalkrishnan *et al*., 2010). 55.5% of Staphylococcus aureus strains were MRSA. The high incidence of MRSA in our study correlates well with studies done by Wattal *et al*. (2010); Joseph *et al*. (2010). The overall picture suggests that number of drug-resistant strains of various organisms is rising and is an important cause of VAP in our setting. ICU is considered as the `Hotspot` for development of resistance. ESBL along with MBL is emerging in VAP infections. There is ample of evidences that ICUs are the epicentres of outbreaks of MDR pathogens.

Conclusion

This study showed that quantitative culture of ETA is a useful test for early diagnosis of VAP and provides specific knowledge of the causal agents associated with VAP along with their sensitivity pattern, which will help as an epidemiological marker for initial prophylactic and treatment planning for mechanically ventilated patients in our ICU setup. This study points towards a precarious situation in which our armamentarium of antibiotics is being rapidly depleting as most organisms are developed resistance to even the new generation antibiotics. This is an eye-opener for all healthcare providers working in the field of intensive care. This will help them to understand the microbiological spectrum of VAP and plan the management as well as preventive strategies accordingly.

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