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Research Article

STUDY OF MULTIDRUG RESISTANT (MDR) ISOLATES IN PATIENTS WITH VENTILATOR ASSOCIATED PNEUMONIA (VAP) IN TERTIARY CARE HOSPITAL

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ABSTRACT

The identification of microorganisms which cause ventilator associated pneumonia (VAP) is important for formulating appropriate therapies. In this study, we have reported the incidence of VAP and the prevalence of multidrug resistant (MDR) microorganisms from patients who were diagnosed with VAP in our medical-surgical intensive care unit (ICU) during the period from July 2013 to May2014.Material and Methods: Patients who were on mechanical ventilation for more than 48hrs and in whom ventilator associated pneumonia was suspected, when a new and persistent pulmonary infiltrate appeared on the chest radiograph and who had at-least two of the following criteria, were included in the study: 1. Fever ≥38°C or hypothermia ≤36°C 2. WBC count ≥10000/mm3 or ≤4000/mm3 and 3. Purulent endotracheal secretion.Results: The incidence of VAP in our hospital setting was found to be 40% and the most frequently isolated pathogens were Acinetobacter species, Klebsiellapneumoniae, Pseudomonas aeruginosa, E.coli and Staphylococcus aureus. Of the 110 isolates which were studied, 57(51.8%) were found to be MDR.Conclusion: In conclusion, the incidence of VAP and the prevalence of multidrug resistant microorganisms were quite high in our ICU setup. A local surveillance program at each centre is essential, as the knowledge of local resistant patterns is vital for selecting the appropriate agents for treating infections.

Keywords: Multidrug, Resistance, Ventilator,Associated, Pneumonia.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is pneumonia that occurs 48 hours or more after endotracheal intubation and mechanical ventilation (MV) that was not intubating at the time of admission, also including pneumonia developing after extubation. [1]

Ventilator associated pneumonia is the most common nosocomial infection which affects patients in the intensive care units (ICUs)[2]. Early onset VAP, which occurs during the first 4 days of MV is usually less severe, associated with a better prognosis and more likely caused by antibiotic sensitive bacteria. Late onset VAP, which develops 5 or more days after initiation of MV, is caused by multidrug resistant (MDR) pathogens and associated with increased mortality and morbidity. [3] The common pathogens causing VAP include aerobic gram negative rods such as Acinetobacter species, Klebsiellapneumoniae, Pseudomonas aeruginosa and Escherichia coli. [1,4,5]. VAP due to methicillin resistant Staphylococcus aureus (MRSA) has been rapidly emerging [4,5].

There is an increasing trend of multiple drug resistant (MDR) isolates in the ICU setup, which considerably increases the morbidity, mortality and the days of mechanical ventilation among the hospitalized patients [6,7,8].The incidence of multi drug resistant (MDR) strains which cause VAP may vary from hospital to hospital, among the types of ICU patients, with

antibiotic use and among different patient populations and comorbid conditions[2,6].The MDR isolates which are present in the ICU and in the hospital environment pose not only therapeutic problems, but also serious concerns for infection control management [7,8]. A local surveillance program is essential at each centre, as the knowledge of local resistant patterns is vital for selecting appropriate agents for treating infections.

So, the present study was undertaken to assess the incidence of the MDR isolates in the patients who developed VAP in our settings.

MATERIAL& METHODS

A total of 100 patients who were admitted to the ICU of the Medicine and Surgery departments were evaluated over a period from July 2013 to May 2014.

Selection of the Patient

The patients who were selected for the study were those who were on mechanical ventilation for more than 48hrs with suspected ventilator associated pneumonia, when a new and persistent pulmonary infiltrate appeared on the chest radiograph and had at least two of the following criteria [2,6,7]:

1. Fever ≥38°C or hypothermia ≤36°C
2. WBC count ≥10000/mm3 or ≤4000/mm3
3. Purulent endotracheal secretion.

Collection of the Endotracheal (ET) Secretion

From patients who fulfilled the above criteriae, ET secretion was collected and it was immediately transported to the Department of Microbiology for further processing.

For a definitive diagnosis of VAP, in this study, the quantitative culture threshold was considered as ≥105cfu/ml [9,10,11,12].Antibiotic sensitivity testing was carried out on Mueller-Hinton agar (MHA) plates by the Kirby Bauer's method for the following antimicrobial agents according to the Clinical and Laboratory Standards Institutes (CLSI) guidelines [13].

Antimicrobial discs used for gram negative isolates are Amikacin 30µg, Gentamicin 10µg, Norfloxacin 10µg, Aztreonam 30µg, Cefotaxime 30µg, Ceftriaxone 30µg, Nalidixic acid 30µg, Nitrofurantoin 300µg, Cefuroxime 30µg, Ciprofloxacin 5µg, Ofloxacin 5µg, Ceftazidime 30µg, Cefixime 5µg, Cefdinir 5µg, Imipenem 10µg, Meropenem 10µg, Levofloxacin 5µg, Piperacillin/Tazobactum 100+10µg, Cefepime 50µg, Amoxyclav 30µg and Colistin 10µg.

Antimicrobial discs used for gram positive isolates are Cefoxitin 30µg , Doxycycline 30µg, Vancomycin 30µg, Linezolid 30µg, Teicoplanin 30µg, Penicillin 10 IU, Amoxycillin 10µg, Amoxyclav 30µg, Co-trimoxazole 25µg, Cefalexin 30µg, Cefazolin 30µg, Cefuroxime 30µg, Erythromycin 15µg, Chloramphenicol 30µg, Ciprofloxacin 5µg, Ofloxacin 5µg, Piperacillin 100µg, Azithromycin 15µg and Tetracycline 30µg.

• MRSA was confirmed by using cefoxitin disc [13] on Mueller-Hinton agar plates with 4% NaCl.

• Suspected ESBLs were identified by the double disk synergy test, by using ceftazidime and the ceftazidime and clavulanic acid combination [13]. [Fig-1]. Increase of ≥5 mm in zone of inhibition for ceftazidime–clavulanic acid disc compared to the ceftazidime alone was taken as confirmatory evidence of ESBL production.

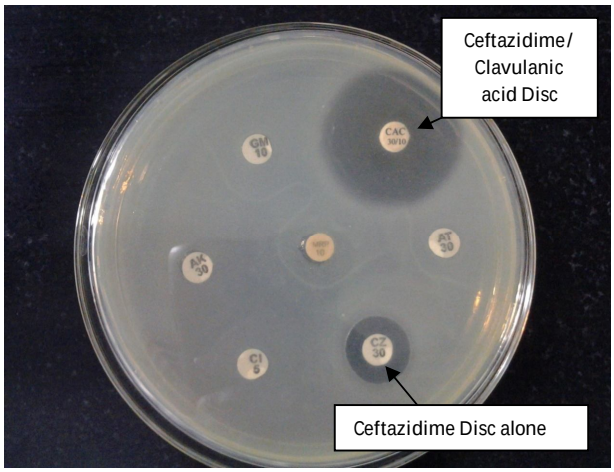

Fig-1 Culture plate showing ESBL resistance

• Suspected AmpCβ-lactamases were screened by checking for a decreased sensitivity to the ceftazidime and the cefoxitin discs [14]. A flattening or indentation of the cefoxitin inhibition zone in the vicinity of the disc with test strains was interpreted as positive.[13]

• MBL producers were identified by the Imipenem-EDTA disc method [15,16].[Fig-2]. Two imipenem discs were placed on the surface of agar plate at distance of 25mm and 750µg of EDTA was added to one of them. After 24 hours of incubation at 37°C, the inhibition zones of imipenem and

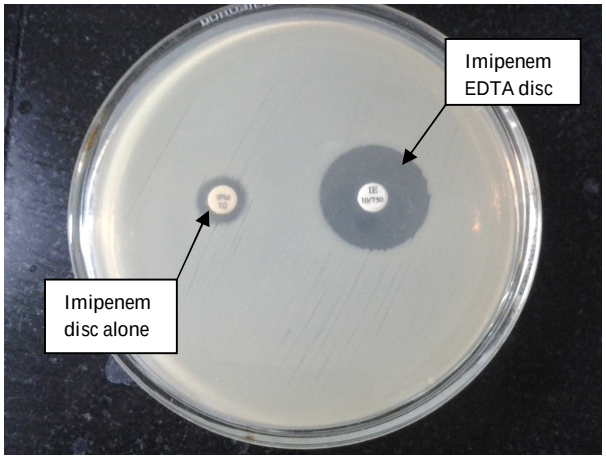

Fig-2 Culture showing sensitivity
(Double disc synergy test)

Imipenem-EDTA disc were compared. If the increase in inhibition zone with the Imipenem-EDTA disc was ≥7 mm than the Imipenem alone, it was considered MBL positive.

VAP pathogens such as Pseudomonas species, Acinetobacter species, and enteric Gram-negative bacilli who expressed ESBL, AmpCβ-lactamases or MBL, and resistant to three or more antimicrobial classes were defined as "multi-drug resistant" (MDR) pathogens [8,11].

RESULTS

A total 100 patients were evaluated during the period from July 2013 to May2014. The quantitative culture results (≥105 cfu/ml) for pathogenic organisms which caused VAP were significant in 40 (40%) patients. 60 (60%) patients were not considered to have VAP, as the quantitative cultures of the ETA showed a colony count of <105 cfu/ml and they were considered as commensals or simply colonization.

The infection was polymicrobial in 24(60%) cases and monomicrobial in 16(40%) cases, while 19(47.5%) were early onset (≤ 5days) and 21(52.5%) were late onset (≥5days) infections. [Table-1] shows the characteristics of the VAP patients. The various underlying conditions are shown in [Table2 and 3].

The most common organisms which were isolated were Acinetobacter species [35(31.8%)], Klebsiellapneumoniae [30(27.3%)], Pseudomonas aeruginosa [25(22.7%)], followed by E.coli [15 (13.6%)], and Staphylococcus aureus [5(4.6%)]. [Table-4]

Of the 35 Acinetobacterspp, 14(40%) were AmpCβ-lactamase producers and they were sensitive to imipenem and meropenem, while no MBL producers were seen.

Table-1 Characteristics of patients with VAP

Characteristics	**Patients developing VAP (40)**
Age (years)	50-80 Years
Sex	
Male	24 (60%)
Female	16 (40%)
VAP onset	
Early (<5 days)	19(47.5%)
Late (≥5 days)	21(52.5%)
ICU	
Medicine	28 (70%)
Surgery	12 (30%)
Infection	
Polymicrobial	24 (60%)
Monomicrobial	16 (40%)

Table: 2 Medicine ICU Cases

S.No.	Diagnosis	Cases	VAP	%
1	ARDS	14	8	57.1%
2	Hypertension & Acute MI	08	5	62.5%
3	Shock & Septicemia	07	5	71.4%
4	COPD	06	4	66.7%
5	Viral Hepatitis	05	2	40%
6	Chronic Renal Failure	04	2	50%
7	CNS Infection	02	1	50%
8	Others	02	1	50%

ARDS – Acute respiratory distress syndrome, MI – Myocardial Infarction, COPD – Chronic obstructive pulmonary disease, CNS – Central nervous system.

Table: 3 Surgical ICU Cases

S.No.	Diagnosis	Cases	VAP	%
1	RTA	13	6	46.1%
2	Intestinal obstruction	07	3	42.8%
3	Brain Tumour	02	1	50%
4	Others	05	2	40%

RTA – Road traffic accidents.

Table: 4 No. Of Isolates

Organism	No. Of Isolates (%)	MDR (%)
Acinetobacter Species	35 (31.8%)	14 (40%)
Klebsiellapneumoniae	30 (27.3%)	21 (70%)
Pseudomonas aeruginosa	25 (22.7%)	9 (36%)
E.coli	15 (13.6%)	11 (73.3%)
Staphylococcus aureus	05 (4.6%)	2 (40%)

The remaining isolates were sensitive to gentamicin, amikacin, ciprofloxacin and ceftazidime.

Of the 30 Klebsiellapneumoniae strains, 11 were (36.6%) ESBL and 10(33.4%) were AmpCβ-lactamase producers. All the strains were sensitive to imipenem, meropenem and piperacillin-tazobactam, while the remaining isolates were sensitive to gentamicin, amikacin, ciprofloxacin and ceftazidime also.

Of the 25 Pseudomonas aeruginosa strains, 4(16%) were MBL and 5(20%) were AmpCβ-lactamases producing strains. All the MBL strains were sensitive to aztreonam, polymyxin B, colistin and piperacillin-tazobactam and all the AmpCβ-lactamases were sensitive to imipenem, meropenem and piperacillin-tazobactam, but they were resistant to azetronam. Of the remaining 16 isolates, 7(43.7%) were resistant to amikacin, 11 (68.8%) were resistant to

ciprofloxacin, 8(50%) were resistant to gentamicin, 12(75%) were resistant to ceftazidime, 7(43.8%) showed resistance to aztreonam and 4 (25%) were resistant to piperacillin/tazobactam.

Of the 15 E.coli strains, 6(40%) were ESBL and 5(33.3%) were AmpCβ-lactamase producers. All the strains of E.coli were sensitive to imipenem, meropenem and piperacillin-tazobactam, while the remaining isolates were sensitive to gentamicin, amikacin, ciprofloxacin and ceftazidime also

Of the 5 Staphylococcus aureus strains, 2(40%) were MRSA and all the MRSA strains were resistant to penicillin and erythromycin, while 100% sensitivity was shown to vancomycin and linezolid.

Of the total 57 MDR isolates, 37 organisms were from late onset VAP, while 20 MDR isolates were from early onset VAP. Pseudomonas aeruginosa was the dominant organism in both the forms of VAP.

DISCUSSION & CONCLUSION

VAP, a form of hospital acquired pneumonia is a serious infection with a high mortality rate and in the literature, the overall incidence of VAP in ICUs ranges from 10-70% [2,6,8,15,17]. In the present study, the incidence of VAP was found to be 40%.

The pathogens which are responsible for VAP vary, depending on the duration of the mechanical ventilation, prior antibiotic exposure and the length of stay in the hospital. Acinetobacter, Klebsiellapneumoniae, Pseudomonas aeruginosa, E.coli and MRSA are the most dominant organisms [7,8]. In our study also, the organisms causing VAP were Acinetobacter species, Klebsiellapneumoniae, Pseudomonas aeruginosa, E.coli and MRSA.

While considering the epicenters of bacterial resistance, ICUs are found to be the main sources of the upsurges in the numbers of MDR. Among the risk factors, the one that has been emphasized is antimicrobial agent abuse, which exerts a selective pressure on certain groups of microorganisms, thus turning them resistant. In addition, the routine use of invasive techniques as well as ICU overcrowding and the increased susceptibility in this population of patients who usually suffer from severe illnesses, further increase the risk of infection with multidrug resistant microorganisms [2, 7, 8].

There is high antibiotic resistance in nosocomial, gram negative pathogens which are isolated from ICUs, which are mostly resistant to ceftazidime, ciprofloxacin, gentamicin and amikacin. Though most of the gram negative organisms show susceptibility to carbepenem, the resistance to imipenem is on a rise, all over the world, by means of metalloβ -lactamase production [16,17,18]. In our study, 51.8% of the isolates were Multidrug resistant. Similar to our study (52.5%), in many other studies, it has been shown that the MDR pathogens were mostly associated with late onset VAP than with early onset VAP [17,18].

The higher incidence of VAP and MDR in our study could be attributed to the presence of co-morbid conditions. Some of the patients were seriously ill with conditions such as road traffic accidents, acute mycocardial infarction, etc. The health seeking behaviour of our patients was different from that which was found in the developed world. Due to limited resources, the patients seek medical help only when it is absolutely inevitable. By the time the patient is referred to the tertiary care centre, his underlying condition becomes well advanced and it may become irreversible. This may necessitate a longer duration of mechanical ventilation which is directly proportional to the development of VAP and subsequently the MDR pathogens.

This emphasizes the need for judicious selection and rational use of appropriate antibiotics which may reduce patient colonization and subsequent VAP by MDR pathogens. Similarly, unnecessary prolonged hospitalization and prolonged intubation and MV of the patient should be avoided as far as possible, rather non-invasive techniques for ventilation should be tried whenever possible. On the basis of antibiotic susceptibility tests of our study and similar other studies, [1] empirical therapy can be broadened to include either an antipseudomonal cephalosporin (cefepime or ceftazadime), a carbepenem (imipenem or meropenem), or a β-lactam/β-lactamase inhibitor (pipercacillin-tazobactam) plus anantipseudomonalfluoroquinolone (ciprofloxacin or levofloxacin), or an aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin.

To conclude, awareness of independent risk factors documented in this study may assist in identifying patients at higher risk for VAP and help in implementing appropriate preventive measures, including proper positioning and patient care and modulating intervention measures during

management. Limitations of this study were small sample size; inadequate determination of risk factors of development of VAP in predisposed person. Also knowledge of the susceptibility pattern of the local pathogens should guide the choice of antibiotics, in addition to the likelihood of organisms, as there is an increasing prevalence of MDR pathogens in late onset VAP.

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