



Original Research Article

Multidrug resistant ventilator associated pneumonia: A persistent and dreaded complication in Indian tertiary care hospitals

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ABSTRACT

Introduction: Like any other Device associated infection, Ventilator Associated Pneumonia also poses a great threat to public health. This study aims to know the prevalence rate of VAP and study the drug resistance pattern of its causative agents.

Materials and Methods: A prospective, observational study involving 480 patients was conducted over a period of twelve months to calculate the prevalence of VAP amongst the intubated patients and to isolate the causative organisms with their resistance patterns for antibiotics.

Results: Among the 480 patients on mechanical ventilation included in this study, sixty patients developed VAP. This amounted to a VAP rate of 31.25 per 1000 ventilator days. Culture yielded Gram negative organisms in 51 samples and Gram positive cocci in 9, majority of which were multi drug resistant organism by the virtue of producing ESBL, AmpC and MBL enzymes.

Conclusion: Identifying VAP and the MDR organisms causing it and formulating a tailored antibiotic therapy is very imperative for the timely treatment and reduction in morbidity and mortality caused by VAP.

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1. Introduction

One of the most common Device associated Infection that has major implications on patient safety globally is Ventilator associated pneumonia (VAP). VAP is associated with increased cost of treatment in addition to increased mortality and other deleterious repercussions and social ramifications on the patients. The emergence of drug resistant bacteria as causative organisms of VAP has aggravated the already alarming situation of increasing VAP cases across Intensive Care Units in Indian hospital. The multi drug resistant (MDR) bugs are extremely difficult to treat and pose a unique challenge to physicians and consultants.¹ The mean rate of VAP was reported to be 5.4 per 1000 ventilator days in the U.S. according to NNIS (National Nosocomial Infections Surveillance) system² whereas the VAP rate in Asian countries was much higher

ranging from 3.5 to 46 per mechanical ventilator days³

Early onset VAP which occurs during first four days of mechanical ventilation is usually less severe, associated with a better prognosis, and is more likely caused by antibiotic sensitive bacteria. Late onset VAP which develops five or more days after initiation of mechanical ventilation is caused by multidrug resistant pathogens and is associated with increased morbidity and mortality.⁴ Typically, bacteria causing early-onset VAP include Streptococcus pneumoniae (as well as other streptococcus species), Hemophilus influenza, methicillin-sensitive Staphylococcus aureus (MSSA), enteric Gram-negative bacilli, Escherichia coli, Klebsiella pneumonia, Enterobacter species, Proteus species and Serratia marcescens. Culprits of late VAP are typically Multi Drug Resistant (MDR) bacteria, such as methicillin-resistant S.aureus (MRSA), Acinetobacter, Pseudomonas aeruginosa, and extended-spectrum beta-lactamase producing bacteria (ESBL).⁵

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It is a proven fact that longer the hospital stay there are more chances of Hospital acquired infection. Kanj SS et al in their study proved that Length of hospital stay was more in patients who acquired VAP.⁶ The hospital stay was 7.3 days for those without device associated infections and 18.8 days for those with VAP.⁷ Furthermore, longer duration of hospital stay (>5 days) and mechanical ventilation were identified as a significant risk factors for acquiring bacterial infections producing ESBL and AmpC enzymes.⁸

With the objective of deducing VAP rate in a tertiary care hospital ICUs in Karnataka, this study was conducted at KIMS hospital, Hubli. This study also aimed at recognising the causative organisms involved and their resistance patterns.

2. Materials and Methods

This is a prospective, observational study conducted over a period of one year. The study population consisted of only those patients who were put on mechanical ventilation in the ICUs. The medical and surgical ICUs served as source of samples- deep tracheal aspirate from the endotracheal tubes collected from patients put on ventilators. To comply with the definition of Ventilator Associated Pneumonia, those patients who were already showing signs and symptoms of pneumonia at the time of admission to hospital or within 48 hours of admission were not included in this study. Significant data regarding patient's stay in ICU, any associated co morbidities, smoking habits, number of days on ventilation, outcome etc were noted down.

After receiving the samples in microbiology laboratory, they were immediately inoculated onto Thioglycollate broth. The samples were also streaked on solid culture media like Blood agar and Mac Conkey agar, which were then incubated for 24 hours. CLSI guidelines were followed in identifying the causative pathogen using appropriate biochemical tests and also reporting its antibiotic susceptibility pattern by using Kirby Baur method of disc diffusion test⁹

We used Ceftazidime 30 microgram disks to screen Gram negative bacilli for production of ESBL enzyme as per CLSI guidelines. Based on the screening results, the positive ESBL isolates were subjected to a confirmatory disc diffusion (phenotypic) test using Ceftazidime disc and a combination of Ceftazidime 30 microgram + Clavulanic acid 10 microgram (CLSI, 2013). A difference of ≥ 5 mm between the zone diameters of ceftazidime disk and the ceftazidime-clavulanate combination disk was taken to be confirmatory for ESBL production.

Similarly, Cefoxitin disk 30 microgram was used to screen the isolates for production of AmpC. Isolates giving a zone of inhibition of less than 18 mm with Cefoxitin were considered as AmpC producers on screening test. These were further subjected to a phenotypic confirmatory AmpC disk test. Metallo Beta Lactamase (MBL) production

was screened by using 10 microgram Imipenem disk. Combined disk test was used as a confirmatory phenotypic test for production of MBL by the screening test positive pathogens (isolates which produced a zone of <19 mm around Imipenem disk)(Behera et al., 2008) (CLSI, 2013). MRSA screening was done by using by Cefoxitin disc diffusion method.

2.1. Calculation of VAP rate

For calculating VAP rates, two parameters were noted down- Number of VAP cases and total number of mechanical ventilator days. VAP rate per 1000 ventilator days was calculated by dividing the total number of VAP infections by the total number of ventilator days and multiplying the result with 1000¹⁰

3. Result

In our study period of one year, 480 patients were intubated with endotracheal tube, of which 60 (12.5%) patients developed VAP. The total ventilator days amounted to 1920 in the study population. A total 60 episodes of VAP occurred in these patients, amounting to a VAP rate of 31.25 per 1000 ventilator days.

Out of the 60 cases of VAP, 37 (61.66%) were males and the rest 23 (38.33%) were females. Associated Co-morbidities were observed among 46 patients. Of these 20 (33.33%) patients were hypertensive, 12 (20.0%) diabetic, 5 (8.33%) suffering from malignancy, 4 (6.66%) HIV seropositive, and 4 (6.66%) chronic alcoholic. Out of 60 patients studied, 4 (6.66%) patients died due to VAP.

Culture yielded Gram negative organisms in 51 samples and Gram positive cocci in 9. The different organisms isolated were *Klebsiella pneumoniae* from 20(33.33%), *Acinetobacter baumannii* 12(20%), *Pseudomonas aeruginosa* 10 (16.66%), *Citrobacter koseri* six(10%), *Escherichia coli* two (3.33%), *Providencia rettgeri* one (1.66%), *Staphylococcus aureus* four (6.66%) and coagulase negative staphylococcus five (16.66%) patients. Out of the total 60 cases, Gram negative bacteria were isolated from 51 (85 %) of the VAP infections. It was further confirmed that 36 (70.59%) of these gram negative isolates were ESBL producing infections, 35 (68.62%) were AmpC producers and 23 (45.10%) were Co-producers of both ESBL and AmpC (Table 1). Among the total 30 *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolated, 4 (13.33%) were MBL producers (Table 2).

Among the 4 *Staphylococcus aureus* isolated from the samples of VAP, 2 were Methicillin resistant *Staphylococcus aureus* (MRSA). However, out of the 5 CoNS, 2 were detected to be MRCoNS by cefoxitin disc diffusion test (Figure 1).

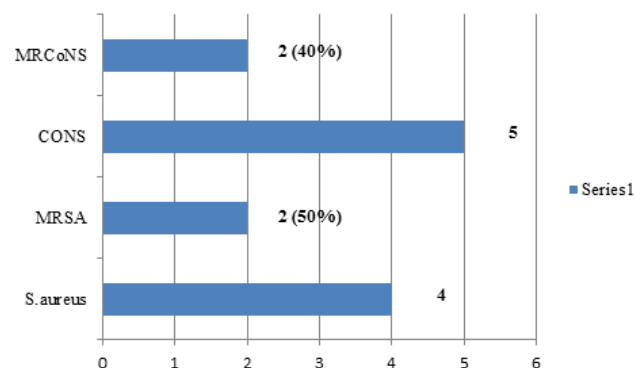
The antibiotic profiles of the VAP pathogens evidently proved that majority of them were multi drug resistant

Table 1: Distribution of various beta lactamases amongst VAP infections

Beta lactamase	Number (Percentage)
ESBL	36 (70.59%)
AmpC	35 (68.62%)
ESBL + AmpC (Co-producer)	23 (45.10%)
Total no of GNB	51 (85.0%)

Table 2: Table depicting MBL positive isolates

Beta lactamase	Number (Percentage)
MBL	4 (13.33%)
Total no of Pseudomonas & Klebsiella	30 (50%)

**Fig. 1:** Graph showing MRSA and MRCoNS positive isolates

by virtue of various mechanisms. Various beta lactamase enzyme producing bacteria were concertedly found to be resistant to penicillins, cephalosporins, tetracycline etc. Despite the multidrug resistance patterns, the silver lining in the profiles was that except for 13% Acinetobacter and 13% Pseudomonas, all other Gram negative bacilli were sensitive to Imipenem. Amikacin was the second most sensitive drug following Imipenem for the gram negative bacilli. Azithromycin, clindamicin, linezolid and vancomycin showed excellent sensitivity on Staphylococci whereas ampicillin presented a completely resistant picture. Table 3 depicts the antibiogram profile of all the VAP isolates.

4. Discussion

Around 8 to 20% of patients admitted in ICU are estimated to be affected by VAP and this number goes upto 27% in patients who are on mechanical ventilation.¹¹ Our study showed a comparatively lower incidence of 12.5% of patients in ICU on mechanical ventilation developing VAP. This could be attributed to various factors like well trained nursing faculties and adherence to preventive bundles. VAP has been proved to be associated with longer duration of stay in ICU, Longer mechanical ventilation, increased morbidity and hospitalisation costs.

Many previous noted studies have documented the risk factors for acquiring VAP. These risk factors include male sex, preexisting pulmonary disease, multiple organ system failure, the presence of intubation or enteral feeding, mechanical ventilation, and supine position, previous use of antibiotics for more than 2 weeks, diabetes etc.^{12,13} Though our study did not mainly focus on the risk factors associated with VAP, 61.66% of patients who developed VAP were males and 20% reported of diabetes as associated co morbidity, thus conforming with the other studies.

The most common causative organisms isolated in this study were Klebsiella pneumoniae (33.33%) followed by Acinetobacter baumannii (20%), Pseudomonas aeruginosa (16.66%), Coagulase negative Staphylococcus (16.66%) and Citrobacter koseri (10%). This finding is in accordance with various other Asian studies which reported prevalence of Gram negative bacteria especially Pseudomonas, Acinetobacter and Klebsiella as the major pathogens isolated from VAP.³ The severity of VAP problem is further increased if the isolated organisms turn out to be multi drug resistant. These resistant infections put a tremendous pressure on Health care system of a developing nation which is already battling with limited resources. Our study showed a high rate of multi drug resistant organisms isolated from the VAP cases. Gram negative bacilli were responsible for 85% (ie 51 cases) of VAP infections in our study. Extended spectrum beta lactamase production was confirmed in 70.59% of these gram negative isolates whereas the AmpC production was detected in 68.62%. A considerable number of gram negative isolates 23 (45.10%) were found to be producers of both ESBL and AmpC (Co-producers). The most effective antibiotic for these were found to be Imipenem and Amikacin. However, the most dreadful situation is production of MBL enzymes. Among the total 30 Pseudomonas aeruginosa and Klebsiella pneumoniae isolated, 4 (13.33%) were MBL producers.

This study adds to the growing information on prevalence of VAP in healthcare settings and the menace of MDR organisms. It is important to know that VAP is preventable. American thoracic society has laid down guidelines for preventing VAP and decreasing VAP rates in hospitals.

Table 3: Antibiotic Resistance pattern of VAP isolates (%)

Organism Antibiotic	Klebsiella	Acinetobacter	Pseudomonas	Citrobacter	E.coli	Staphylococcus
Amikacin	34	83	83	50	50	67
Ampicillin	100	100	100	100	100	100
Amoxicillin clavulanate	68	100	100	33	50	44
Cefazolin	100	100	100	50	100	-
Cefepime	100	100	100	33	100	67
Cefoxitin	67	100	100	50	68	44
Cefotaxime	67	100	100	33	70	-
Ceftazidime	67	100	83	33	70	-
Ceftriaxone	67	100	100	33	70	-
Ciprofloxacin	88	83	100	33	75	44
Cotrimoxazole	88	83	100	67	75	-
Gentamicin	67	83	83	50	50	67
Imipenem	0	13	13	0	0	-
Tetracycline	83	100	100	50	100	-
Azithromycin	-	-	-	-	-	0
Clindamicin	-	-	-	-	-	0
Erythromycin	-	-	-	-	-	0
Linezolid	-	-	-	-	-	0
Vancomycin	-	-	-	-	-	0

Table 4: Risk factors for development of VAP

1. Predisposing acute or chronic lung pathology 2. Intubation 3. Supine position 4. Enteral feeding 5. Age > 60 years 6. Diabetes 7. Glasgow coma scale < 9 8. Excessive sedation 9. Cigarette smoking

These (VAP bundle) include¹¹

1. Minimal use of invasive devices
2. Strict hand hygiene with alcohol based rubs
3. Judicious use of antibiotics
4. Sublottic secretions should be continuously aspirated
5. Detection of pneumonia and deescalation of drug treatment
6. Preferred use of oral tubes than nasal endotracheal tubes
7. Maintenance of endotracheal cuff pressure . 20 cm H20
8. Limited use of sedative and paralytic agents
9. Positioning of the patient - Semirecumbent positioning (30 to 45 degrees) is recommended to reduce the risk of aspiration.
10. Adequate nurse-to-patient ratios
11. Staff education

The antibiotic therapy for treating VAP cases should be tailored based on microbiological data rather than empirical formula which increases the potential for antibiotic overuse, emergence of resistance, unnecessary adverse effects and potential toxicity leading to increased cost, hospital stay and morbidity. Antibiotic stewardship programs are the need of hour in controlling multi drug resistant infections in health care settings.

5. Source of funding

None.

6. Conflict of interest

None.

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