

**Original Article**

## **BACTERIOLOGICAL STUDY OF VENTILATOR-ASSOCIATED PNEUMONIA AND ANTIBIOTIC SUSCEPTIBILITY OF ISOLATES**

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### **ABSTRACT**

**Objective:** The present study determined the prevalence of various aerobic bacteria causing ventilator-associated pneumonia in adult patients. Initially the bacteria causing ventilator-associated pneumonia was isolated from ET samples and studied the antimicrobial susceptibility pattern of bacterial isolates.

**Methods:** Total 250 endotracheal aspiration (ET) samples were collected from patients admitted in Medical, Respiratory and Surgical ICUs for 1 y period. ET aspirates were collected under aseptic precautions and processed as per standard operating procedure for the identification of microorganisms. The antibiotic susceptibility test was performed by using Kirby-Bauer disk diffusion method as per CLSI guidelines.

**Results:** Out of the 250 samples processed, culture-positive were 34.8% (n=87) and culture-negative were 65.2% (n=163). Out of 87 culture-positive samples, polymicrobial growth was observed in 9.19% (n=8) and monomicrobial growth was observed in 90.8% (n=79). Gram negative bacilli 95.7% (n=91), and gram-positive cocci isolates are 4.2% (n=4). Among Gram-negative organisms isolated, *A. baumannii* is the most common isolate 33 (34.7%), followed by *P. aeruginosa* 28 (29.5%) and *K. pneumoniae* 20 (21.0%) *E. coli* 8 (8.4%) and *E. cloacae* 2 (2.1%). Out of 4 Gram-positive organisms isolated, 3 (3.1%) were MSSA, and 1(1.1%) was MRSA.

**Conclusion:** VAP is increasingly associated with multidrug-resistant (MDR) pathogens due to the production of ESBL, Amp C  $\beta$ -lactamase, Metallo- $\beta$ -lactamase. It is important to carry out aggressive surveillance to determine the prevalence of MDR organisms and to generate a local antibiogram periodically. Early and appropriate antibiotics in right doses followed by de-escalation based on microbiological culture results are essential to curtail the VAP rate. VAP bundle care shall be implemented correctly.

**Keywords:** Ventilator associated pneumonia, Multi-drug resistant organisms, Hospital-acquired infections, ESBLs, Amp C, Metallo- $\beta$ -lactamase

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### **INTRODUCTION**

Ventilator-Associated Pneumonia (VAP) is the most common device-associated hospital-acquired infection (HAI) among patients who are mechanically ventilated in the Intensive care units (ICU) and important cause of morbidity and mortality despite advances in Antimicrobial therapy better supportive care modalities. American Thoracic Society and Infectious Diseases Society of America jointly defined VAP as pneumonia in patients with mechanical ventilation for at least 48 h and characterized by the presence of a new or progressive infiltrate, signs of systemic infection (temperature, blood cell count), changes in sputum characteristics and detection of causative agent [1]. VAP infection is being affected 8–20 % of all ICU patients and up to 27% of mechanically ventilated patients [2]. It occurs due to the micro-aspiration of secretions that accumulate around the ventilator device or the inhalation of contaminated aerosols, resulting in inflammation of lung parenchyma. These secretions harbor significant concentrations of the mixed bacterial flora that may contain antimicrobial-resistant bacterial pathogens [3]. Clinical signs and symptoms include the presence of new or progressive radiographic infiltrate and at least two of the three clinical features such as temperature >38 °C or hypothermia, leukocytosis/leukopenia or purulent respiratory secretions [4]. Early-onset pneumonia occurs within four days is less severe and caused by organisms like methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Late-onset VAP occurs after four days and is associated with multidrug-resistant organisms.

### **MATERIALS AND METHODS**

The cross sectional study conducted in department of Microbiology, Tertiary care hospital. Total 250 endotracheal

aspiration (ET) samples were collected from patients admitted in Medical, Respiratory and Surgical ICUs for 1 y period. ET aspirates were collected under aseptic precautions and processed as per standard operating procedure for identification of microorganisms. The antibiotic susceptibility test was performed by using the Kirby-Bauer disk diffusion method as per CLSI guidelines. Among Gram positive isolates, Penicillin (10U), Erythromycin (15 $\mu$ g), Gentamicin (10 $\mu$ g), Cefoxitin (30 $\mu$ g), Linezolid (30 $\mu$ g), Amikacin (30 $\mu$ g), Cotrimoxazole (1.25/23.75 $\mu$ g) and Clindamycin (2 $\mu$ g) were used for Antimicrobial susceptibility test. Vancomycin susceptibility for MRSA was detected by doing the MIC test with Vancomycin E-strip (Biomerieux). For Gram-negative bacteria, Amikacin 30 $\mu$ g, Ampicillin 10  $\mu$ g, Cefazolin 30  $\mu$ g, Ciprofloxacin 5  $\mu$ g, Cefotaxime 30  $\mu$ g, Gentamicin 100 $\mu$ g, Cefaperazone+Sulbactam 30/10 $\mu$ g, Piperacillin+Tazobactam 100/10  $\mu$ g, Meropenem 10  $\mu$ g, Colistin 10  $\mu$ g were used to detect antimicrobial susceptibility test.

### **Limitation**

- Molecular techniques could not used to detect the various ESBL, Amp C, and MBL genes in isolated organisms.
- Micro broth dilution testing for Colistin could not be performed

### **RESULTS**

A total of 250 patients mechanically ventilated in MICU, RICU, and SICU for more than 48 h and clinically suspected of having VAP. The majority of patients in the study were males, 72.4% (n=181), compared to the females 27.6% (n=69). The study population comprised of a wide range of age groups from 20-89 y with majority

of patients belonging to the age group 60-69(25.2%) followed by 50-59 (19.2%) and 40-49(18.4%). And 86.4% (n=216) of the patients underwent emergency intubation, 71.2% (n=178) had prolonged ICU stay, and 10.4% of patients had to be re-intubated. Among medical indications, the most common illness responsible for mechanical ventilation was organophosphorus poisoning 45.3% (n=69) followed by respiratory failure 21.7% (n=33) and CVA 23 15.1% (n=23).

Out of the 250 samples, culture positive were 34.8% (n=87) and culture negative were 65.2% (n=163). Out of 87 culture-positive samples, polymicrobial growth was observed in 9.19% (n=8) and monomicrobial growth was observed in 90.8% (n=79). Majority of organisms isolated were Gram-negative bacilli 95.7% (n=91) and gram-positive cocci isolates are 4.2% (n=4) (fig 1).

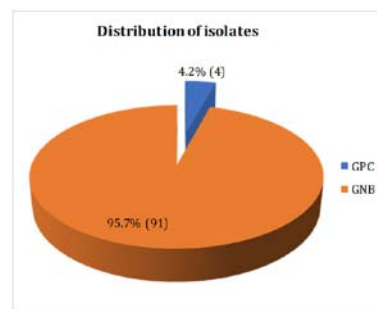


Fig. 1: Showing the frequency of gram-positive and gram-negative isolates

Table 1: Different aerobic bacterial organisms isolated from the culture-positive samples:

Organism	Number	Percentage
Gram-positive	4	4.21
MSSA	3	3.15
MRSA	1	1.05
Gram negative	91	95.78%
<i>Acinetobacter baumannii</i>	33	34.73%
<i>Pseudomonas aeruginosa</i>	28	29.47%
<i>Klebsiella pneumoniae</i>	20	21.05%
<i>Escherichia coli</i>	8	8.42%
<i>Enterobacter cloacae</i>	2	2.10%
Total	95	100

Among Gram-negative organisms isolated, *A. baumannii* is the most common isolate 34.7% (n=33), followed by *P. aeruginosa* 29.5% (n=28) and *K. pneumoniae* 21% (n=20). *E. coli* 8.4% (n=8) and *E. cloacae* 2.1% (n=2). Out of 4 Gram-positive organisms isolated, Methicillin Sensitive *Staphylococcus aureus* (MSSA) were 3.1%(n=3), and Methicillin-Resistant *Staphylococcus aureus* (MRSA) were 1.1%(n=1) (fig. 2).

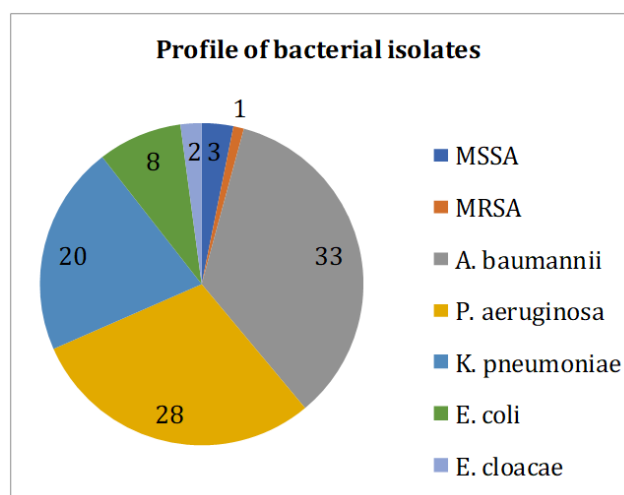


Fig. 2: Showing the prevalence of various bacterial agents in VAP

Among 33 isolates of *A. baumannii*, all the isolates were resistant to Ampicillin and Cefazolin. 97% (n=32) isolates were resistant to Ciprofloxacin, 94% (n=31) isolates were resistant to Cefotaxime. Amikacin and Gentamicin resistance of isolates were 91% (n=30) and 88% (n=29), respectively. Piperacillin+Tazobactam and Cefoperazone+sulbactam were resistant in 88% (n=29) and 94% (n=31), respectively. 57.5% (n=19) isolates were resistant to meropenem.

Among 28 isolates of *P. aeruginosa*, 53.5%(n=15) isolates were resistant to ciprofloxacin, 50%(n=14) were resistant to Cefotaxime (3<sup>rd</sup> generation Cephalosporin), 57% (n=16) were resistant to amikacin, 67.8%(n=19) resistant to gentamicin, 32%(n=9) were resistant to Piperacillin+Tazobactam and 21.4%(n=6) isolates were resistant to Meropenem.

Among the 20 isolates of *K. pneumoniae*, all were resistant to ampicillin, and 95%(n=19) were resistant to cefazolin, 85%(n=17) isolates were resistant to Ciprofloxacin, 80%(n=16) were resistance to cefotaxime, 75%(n=15) were resistant to gentamicin and 45% (n=9) amikacin resistance, 45%(n=9) isolates were resistant to Cefoperazone+sulbactam, 5 (25%) isolates were resistant to Piperacillin+Tazobactam and 20% (n=4) were resistant to meropenem

Among the 8 isolates of *E. coli*, all isolates were resistant to Ampicillin, Cefazolin, and Ciprofloxacin. Among them, 75% (n=6) are resistant both gentamicin and amikacin. Cefoperazone-sulbactam and Piperacillin-tazobactam resistance shown in 37.5% (n=3). All isolates are sensitive to Meropenem.

The 2 isolates of *E. cloacae* obtained were resistant to Ampicillin and Cefazolin. 50% were resistant to Ciprofloxacin, Gentamicin,

Amikacin, Cefotaxime, Cefoperazone-sulbactam, Piperacillin-Tazobactam and Meropenem.

**Table 3: Showing drug resistance of isolates to various antibiotics among Gram-negative organisms**

Antibiotic	No of isolates tested	No. of resistant isolates	Percentage of resistance
Ampicillin	63	63	100%
Cefazolin	63	62	98.4%
Ciprofloxacin	91	73	80.2%
Cefotaxime	91	69	75.8%
Gentamicin	91	70	76.9%
Amikacin	91	62	68.1%
Cefoperazone+Sulbactam	63	44	69.8%
Piperacillin+Tazobactam	91	47	51.6%
Meropenem	91	30	32.9%

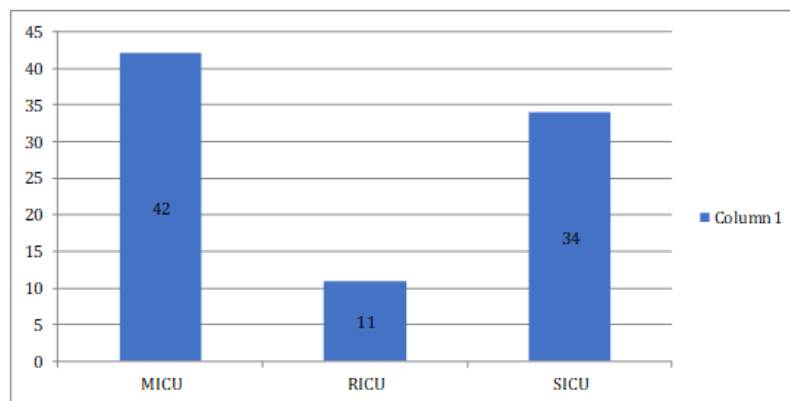
In the present study, the percentage of antibiotic resistance to Meropenem (32.9%), followed by Piperacillin+Tazobactam (51.6%), Amikacin (68.1%), Cefoperazone+Sulbactam (69.8%) and Cefotaxime (75.8%). They have higher degree of resistance towards Ampicillin (100%) followed by Cefazolin (98.4%), Ciprofloxacin (80.2%) and Gentamicin (76.9%) (table 3).

Among the 3 MSSA isolates, all were resistant to penicillin and Erythromycin. The single MRSA isolate was resistant to Penicillin, Erythromycin, Gentamicin, and cotrimoxazole.

Among 33 isolates of *A. baumannii* isolates, carbapenem-resistant were 57.5% (19) and Amp C producers were 36.3% (n=12). Out of the 28 *P. aeruginosa* isolates, ESBL producers were 17.8% (n=5), Amp C  $\beta$ -lactamase producers were 14.2% (n=4), and Carbapenem-resistant were 21.4%(n=6). Among *K. pneumoniae* isolates, ESBL

producers were 33.3% (n=6), Amp C producers were 20% (n=4), carbapenemase producers were 20%(n=4). Among *E. coli* isolates, ESBL producers were 62.5%(n=5), Amp C producers were 25%(n=2).

Among the 91 Gram-negative bacteria isolated, 70 (76.9%) were multi-drug resistant (MDR) organisms. Among MDR isolates 93.9% (n=31) were *A. baumannii*, 53.6%(n=15) *P. aeruginosa* isolates, 80%(n=16) *K. pneumoniae*, 87.5%(n=7) *E. coli* 50% (n=1).



**Fig. 3: Showing distribution of patients in different ICUs**

#### Distribution of patients in ICUs

Out of 87 patients were admitted to the Medical ICU 42 (48.3%), Respiratory ICU-11 and Surgical ICU-34. Among the 42 isolates from MICU, *A. baumannii* was the most common isolate 42.5% (n=20), followed by *P. aeruginosa* (27.6%) and *K. pneumoniae* (21.3%). MSSA and *E. coli* were the other organisms isolated. In RICU, *K. pneumoniae* is the most common organism, 38.5% (n=5), followed by *P. aeruginosa* 30.8% (n=4) and *A. baumannii* 23.1% (n=3). In the SICU, *P. aeruginosa* 31.4% (n=11) was the most common organism isolated, followed by *A. baumannii*28.6% (n=10) *E. coli*17.1% (n=6) and *K. pneumoniae* 14.3% (n=5).

Out of the 23 MDR organisms isolated, *A. baumannii* (39.1%, n=9) is the most common organism, followed by *P. aeruginosa* (21.7%, n=5). Out of the 87 patients, 28 patients have not responded to the treatment, while 59 patients recovered and discharged.

#### DISCUSSION

This study was done to determine the bacterial pathogens involved in VAP and finding the antibiotic susceptibility pattern of the isolates in a tertiary care hospital South India. Male predominance was

observed in the present study and the male: female ratio was 72.4:27.6. And majority of patients belong to age group was 60-69 y (25.2%), followed by 50-59 y (19.2%) and 40-49 y (18.4%). Hence more than 50% of VAP cases occurred in patients above 50 y.

In the present study, high percentage of ET samples received from emergency intubation (86.4%, n=216) followed by prolonged mechanical ventilation (71.2%, n=178) and reintubation (10.4%, n=26). Chances of infection may be due to impaired reflexes after prolonged intubation or due to the altered level of consciousness, which increases the risk of aspiration. The mean duration of mechanical ventilation days in the present study were 13.25 d. These findings are similar to Rello *et al.* study where the mean duration of ventilation was around 10 d [5].

Most common indication for mechanical ventilation in present study being medical causes (60.3%, n=152), followed by neurological trauma (39.2%, n=108). The present study, correlating with Mukhopadhyay *et al.*, reported that medical illness was seen in 61.9% cases of VAP while the remaining 38.1% had the surgical disease [6]. And most common medical illness responsible for mechanical ventilation was organophosphorus poisoning (45.3%),

followed by respiratory failure (21.7%) and CVA (15.1%). Ranjit *et al.* reported 30.43% of cases due to organophosphorus poisoning [7]. Saravu *et al.* reported a higher number of organophosphorus poisoning cases that required prolonged ventilation [8]. Dey *et al.*, reported 2% of cases were due to organophosphorus poisoning [9].

Out of the 87 ET samples, total of 95 organisms were isolated and 95% (n=91) were Gram negative bacilli followed by 4.2% (n=4) Gram positive cocci. Among Gram negative bacilli, *A. baumannii* 34.7% (n=33), followed by *P. aeruginosa* 29.5% (n=28), *K. pneumoniae* 21% (n=20), *E. coli* 8.4% (n=8) and *E. cloacae* 2.1% (n=2). Among Gram positive cocci, MSSA 3.1% (n=3) and MRSA 1% (n=1). The present study correlated with Dey *et al.*, reported *A. baumannii* (48.94%), followed by *P. aeruginosa* (25.53%), *K. pneumoniae* (12.77%), and *E. coli* 10.64%. Bahrami H *et al.* study reported that *A. baumannii* (36.5%), followed by *P. aeruginosa* (15.07%), *K. pneumoniae* (7.1%), *E. coli* (7.1%) and *S. aureus* (24.6%) [10]. Ranjan *et al.*, 95.7% of bacterial isolates were found to be Gram negative bacilli, and 4.28% were Gram positive cocci. *Acinetobacter spp.*, accounted for 34.28% of VAP cases followed by *P. aeruginosa*, which was responsible for 25.71% cases [11].

In the present study, early-onset VAP were 50.5% (n=48), and late-onset VAP were 49.4% (n=47). A study conducted by Golia *et al.* showed that 40.6% of isolates were obtained from early-onset VAP, and 59.3% isolates were obtained from late-onset VAP [12]. A study by Joseph *et al.*, showed that common causative agents of early onset VAP were members of Enterobacteriaceae (25%) and *Acinetobacter spp.* (25%) [13]. A study conducted by Saravu *et al.* showed that in late onset VAP, the most common organism was *A. baumannii* (36.1%), followed by *P. aeruginosa* (27.6%), *Klebsiella spp.* (10.6%). A study conducted by Ranjit *et al.* *A. baumannii* (36.6%) was the most prevalent isolate followed by *P. aeruginosa* (20%), *K. pneumoniae* (13.3%). Similar findings were observed by Joseph *et al.*, Mukhopadhyay *et al.*

Of the total culture-positive isolates, 87 (91.5%) were monomicrobial, and 8 (8.42%) were polymicrobial (mixed pathogens). *A. baumannii* and *K. pneumoniae* were most commonly isolated from mixed infections. Our results were comparable to a study conducted by Thakuria *et al.*, in which 5.66% of VAP isolates were polymicrobial, and 94.3% were monomicrobial [14].

In present study of the 87 patients, 48.3% (n=42) patients were admitted to MICU. *A. baumannii* (42.5%, n=20) was the most common organism, followed by *P. aeruginosa* (27.6%, n=13), *K. pneumoniae* (21.3%, n=10), and MSSA (4.3%, n=2). Ahmed *et al.* reported that in MICU, non-fermenters (*P. aeruginosa* and *Acinetobacter spp.*) contributed to 48.93% [15]. In present study, 34 patients (39.08%) were developed VAP in SICU, 35 organisms were isolated. Out of them, *A. baumannii* were 28.6% (n=10), *P. aeruginosa* were 31.4% (n=11), *E. coli* were 17.1% (n=6), *K. pneumoniae* 14.3% (n=5), *E. cloacae* 2.9% (n=1), MSSA (n=1) and MRSA (n=1). In a study of VAP conducted in ICU by Mehendiratta *et al.*, 37 pathogens were isolated, and *A. baumannii* was the most commonly isolated pathogen (24.3%).

Among them, 70 (76.9%) were MDR organisms. A study conducted by Joseph *et al.*, 78.7% of VAP pathogens were multidrug-resistant organisms. Dominic *et al.* observed that 52.57% of isolates were found to be multidrug resistant, which comprised 59% of *K. pneumoniae* and 66% of *A. baumannii* [17]. In early-onset VAP 33 (68.75%) were MDR organisms, and in late onset VAP, 37 (78.7%) of the organisms were MDR. *A. baumannii* was the most frequently isolated MDR pathogen both in early (36.4%) and late onset VAP (51.3%). In a study by Saravu *et al.*, among early onset VAP, 70.4% had MDR organisms, whereas in late onset VAP, 84% had MDR organisms. In present study, among 87 patients, 96.6% (n=84) patients had received empirical antibiotics, and 3.44% (n=3) did not received any empirical treatment. Patients who were on empirical antibiotics (67.9%, n=57) had MDR isolates in bacterial culture. Among MDR organisms, 57.5% (n=19) were Carbapenamase producers, and 36.3% (n=12) were AmpC producers. Rit *et al.* showed that 50% *A. baumannii* were resistant to the carbapenem group of antibiotics [18].

In present study, while comparing the microbial profile in various ICUs, it is seen that in MICU *A. baumannii* (51.35%, n=19) was the

commonest MDR organism followed by *P. aeruginosa* (21.62%, n=8) and *K. pneumoniae* (21.62%, n=8) and *E. coli* 2 (5.4%, n=2). The present study correlating with Dey *et al.*, in which *Acinetobacter spp.*, (48.94%) were found to be the commonest isolate followed by *P. aeruginosa* (25.53). Dey *et al.* demonstrated that 30.43% produced AmpC among *A. baumannii*. Joseph *et al.* demonstrated that 67% of *K. pneumoniae* were ESBL producers, and 33.3% were AmpC producers. Ahmed *et al.* have reported a Meropenem resistance of 42.8%. Chi *et al.* and Dey *et al.* reported a high prevalence of ESBLs. 84 of the patients were empirically managed with combinations of Piperacillin-Tazobactam, Cefoperazone-Sulbactam, Cefotaxime, Levofloxacin, and Metronidazole. Patients who were not responding to above treatment, meropenem and amikacin combination were given.

Aerosolized Colistin, Polymyxin B, or Aminoglycosides may be considered as potential additional antibiotics in patients with multidrug-resistant Gram-negative bacilli [19]. Aerosolization may increase antibiotic concentrations at the site of infection and may be particularly useful for the treatment of organisms that have high MICs to systemic antimicrobial agents [20]. Out of the 87 patients, 28 (32.2%) did not respond to the treatment and it succumbed to death, while 59 (67.8%) were discharged after treatment. In a study conducted by Ahmed *et al.*, the crude mortality rate of VAP patients was 33.3% (n=36). Infection with MDR isolates significantly affects prognosis in VAP patients. Hence, VAP was associated with higher mortality, increased requirement for tracheostomy, longer duration of mechanical ventilation, and ICU stay.

## CONCLUSION

In order to prevent VAP rate, continuous surveillance has been required for patients admitted in the ICU and on mechanical ventilation. The antibiotic susceptibility pattern of these isolates based on sensitivity reports will be helpful to the clinicians to choose the appropriate antimicrobial agents. The quantitative culture technique for the management of VAP avoids the problem of overtreatment by separating colonizers from infecting pathogens. VAP rate being increased with MDR pathogens due to the production of ESBL, Amp C  $\beta$ -lactamase, Metallo- $\beta$ -lactamase. It is essential to generate a local antibiogram periodically based on the susceptibility profile of the causative organisms at the tertiary care center. VAP bundle care shall be implemented to prevent VAP. Combined approaches of rotational antibiotic therapy and education programs might be beneficial to combat high antibiotic resistance.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally

## CONFLICT OF INTERESTS

Declared none

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