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Original Article

Role of Multidrug-resistant Pathogens in Ventilator-Associated Pneumonia in a Tertiary Care Hospital in India

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Abstract

Aim: Ventilator-associated pneumonia (VAP) is the second most common infection acquired in the intensive care unit (ICU). Bacteriological profiles cause VAP and their susceptibility patterns vary in different institutions.

Methods: A prospective study was conducted from June 2017 to May 2018 in a tertiary care hospital as per the recent NHSN guidelines in finding the incidence of VAP and further determining the etiological agents by both conventional and automated methods. The combination disk method (Phenotypic confirmatory test), ampicillin C (AmpC) disk test, modified carbapenem inactivation method, imipenem/ethylenediamine tetraacetic acid combined disc test, and cefoxitin disk test were performed for the detection of extended-spectrum beta-lactamases (ESBL), AmpC β-lactamases, carbapenemases, metallo-beta-lactamases (MBL), and methicillin-resistant *Staphylococcus aureus*, respectively.

Results: Among 104 patients, 31 cases developed PVAP (possible VAP) during their ICU stay; of these cases, two patients had two episodes of VAP each, and the incidence of VAP was 32%. The most common isolate was *Acinetobacter baumannii* (38%), followed by *Pseudomonas aeruginosa* (22%), *Klebsiella pneumoniae* (16%), and *Escherichia coli* (13.51%). Twenty (54%) of the 37 VAP pathogens were multidrug resistant. ESBL was produced by 40% and 67% of *E. coli* and *K. pneumoniae,* respectively. MBL was produced by 25% of *P. aeruginosa*. In addition, AmpC beta-lactamases were produced by 18% each of the Enterobacteriaceae and non-fermenters, respectively. One of the two *S. aureus* isolates was methicillin-resistant.

Conclusion: The majority of VAP cases in our setting were caused by highly resistant strains. The frequency of specific multidrug resistance pathogens causing VAP may vary due to hospital, patient population, exposure to antibiotics, type of ICU patients, and changes over time, emphasizing the need for timely local surveillance data.

Keywords: Ventilator-associated pneumonia, Extended-spectrum beta-lactamase, Modified carbapenem inactivation method, Intensive care unit, Metallo-beta-lactamase, Multidrug resistance

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Introduction

Ventilator-associated pneumonia (VAP) refers to bacterial pneumonia developed in patients who have been mechanically ventilated for more than 48 hours (1). Although mechanical ventilation is a life-saving intervention, it has its own potential complications. Newer antibiotics in the past decade have not decreased VAP-associated mortality in critical care facilities across the world (2).

Gram-negative organisms such as *Pseudomonas* spp., *Acinetobacter* spp., *Escherichia coli (E. coli)*, and *Klebsiella pneumoniae*, along with Gram-positive organism *Staphylococcus aureus* (*S. aureus*) were identified as the common VAP pathogens with varying prevalence rates. *Pseudomonas* spp., *Acinetobacter* spp., and Enterobacteriaceae are often multidrug resistant due to the production of extended-spectrum beta-lactamases (ESBL), ampicillin C (AmpC) β-lactamases, or metallo-β-lactamases (MBL) (3). This nosocomial infection increases morbidity and likely mortality, as well as the cost of health care (4). The initial empirical therapy can be modified based on the knowledge of local microbiological data, patient characteristics, and sensitivity patterns of expected pathogens in the institution (5).

This study was conducted to elucidate the bacteriological profile and antimicrobial resistance pattern of VAP among mechanically ventilated patients attending the respiratory intensive care unit (RICU) Department of Gandhi Hospital. The objectives of this study were to identify the pathogens and determine their antibiotic susceptibility patterns in addition to identifying multidrug resistance (MDR) by the presence of ESBL, AmpC β-lactamases, carbapenemases,

and MBL in these VAP pathogens.

Materials and Methods

Study Design

This prospective study was conducted in the RICU of a tertiary care hospital in India from June 2017 to May 2018.

Setting

The Departments of Microbiology, Anesthesiology, and Critical Care were involved in this study. The study population included patients requiring ventilation who were admitted to the RICU.

Subject and Sample Size

Overall, 204 patients admitted to the RICU were prospectively evaluated during the study period. Among them, 28 patients (13.72%) were not intubated and thus were excluded from the study. Among those requiring mechanical ventilation, 72 (35.29%) patients were mechanically ventilated for less than 48 hours; therefore, they were excluded from the study. In general, 104 (50.98%) patients, who were mechanically ventilated for more than 48 hours, were monitored daily.

Data Collection Procedure

All the included patients were monitored using the recent clinical and microbiological criteria of the Center for Disease Control and Prevention and National Healthcare Safety Network (NHSN) at frequent intervals for the ventilator events until either discharge or death.

Criteria for VAP Diagnosis

Oxygen demand on the ventilator was measured by the fraction of inspired oxygen or positive end-expiratory pressure. Criteria for defining ventilator-associated conditions (VAC), infection-related ventilator-associated complications (IVAC), and possible VAP were considered by recent NHSN guidelines as described in our previous article (6).

Microbiological Techniques

Specimen Collection

Endotracheal aspirate, which is a non-invasive method, was chosen as a sample in the patient qualifying IVAC criteria.

Methods

The organisms isolated by quantitative culture were identified based on standard bacteriological procedures, including colony morphology and biochemical reactions such as oxidase, catalase, triple sugar iron, citrate, urease, and motility (7). The susceptibility of the clinical isolates to routinely used antibiotics was determined by the Kirby-Bauer disk diffusion method (8). Ampicillin (10 mcg), gentamicin (10 mcg), amikacin (30 mcg), ceftazidime (30 mcg), ceftriaxone (30 mcg), ciprofloxacin (5 mcg), meropenem (10 mcg), ticarcillin (75 mcg), and trimethoprim-sulphamethoxazole (25 mcg) were tested for Enterobacteriaceae. Further, amikacin (30 mcg), gentamicin (10 mcg), ciprofloxacin (5 mcg), piperacillin-tazobactam (100/10 mcg), ceftriaxone (30 mcg), ceftazidime (30 mcg), meropenem (10 mcg), ticarcillin (75 mcg), and trimethoprim-sulphamethoxazole (25 mcg) were tested for *Pseudomonas* and *Acinetobacter* species. Moreover, penicillin (10 units), cefoxitin (30 mcg), tetracycline (30 mcg), ciprofloxacin (5 mcg), erythromycin (15 mcg), clindamycin (2 mcg), vancomycin (30 mcg), linezolid (30 mcg), and trimethoprim-sulphamethoxazole (25 mcg) were tested for *S. aureus*. All the antibiotics were purchased from HiMedia (India). All these antibiotics were chosen for a particular organism as per recent Clinical and Laboratory Standards Institute (CLSI) guidelines from CLSI document M100S (11). Quality control for antibiogram was taken as *S. aureus* ATCC 25923 and *E. coli* ATCC 25922 for gram-positive and gram-negative organisms, respectively. Identification and AST were also performed by the *VITEK® 2* (bioMerieux) automated method.

ESBL production among the members of Enterobacteriaceae was tested with the CLSI phenotypic disk diffusion confirmatory test using both cefotaxime (30 µg) and ceftazidime (30 µg) disks alone and in combination with clavulanic acid (10 µg). Five mm or more increase in the zone of inhibition for either cefotaxime-clavulanic acid (30/10 µg)) or ceftazidime-clavulanic acid (30/10 µg) disk, compared to the cefotaxime or ceftazidime disk alone was taken as the confirmatory evidence of ESBL production, respectively (9). *K. pneumoniae* ATCC700603 and *E. coli* ATCC 25922 were used as QC as per CLSI guidelines. Phenotypic methods for MDR detection is summarised in Table 1 and each one has been described below.

AmpC disk test was performed for the detection of AmpC lactamase (10). A flattening or indentation of the cefoxitin (30 µg) inhibition zone in the vicinity of the disk with the test strain was interpreted as positive for the production of AmpC β-lactamase, while an undistorted zone was considered negative.

Modified carbapenem inactivation method (mCIM) was performed to detect carbapenemase (11). The diameter of the zone of inhibition around each MEM disk was measured, and a zone diameter of 6-15 mm or the presence of pinpoint colonies within a 16-18-mm zone was considered positive (carbapenemase production).

Table 1. MDR Detection by Phenotypic Methods

For Gram-negative Organisms	For Gram-positive Organisms
1. ESBL phenotypic disk diffusion confirmatory test	1. Cefoxitin (30 µg) disk diffusion method
2. AmpC disk test	
3. mCIM test	
4. Imipenem/EDTA combined disc test	

Note. MRD: Multidrug resistance; ESBL: Extended-spectrum beta-lactamases; AmpC: Ampicillin C; mCIM: Modified carbapenem inactivation method; EDTA: Ethylenediamine tetraacetic acid.

On the other hand, zone diameters of 16-18 and ≥19 mm were considered indeterminate and negative non-carbapenemase producing, respectively.

Imipenem (IMP)/ethylenediamine tetraacetic acid (EDTA) combined disc test (CDT) was conducted using IMP and IMP with EDTA for the detection of MBL (12). The presence of an expanded growth inhibition zone of IPM and EDTA of >7 mm than IPM was interpreted as positive for MBL production.

Methicillin-resistant *S. aureus* (MRSA) was detected by the cefoxitin (30 µg) disk diffusion method (13). A ≤ 21 mm growth inhibition zone was considered positive, while ≥ 22 mm was considered negative.

Results

The incidence of VAP by recent NHSN guidelines and its bacteriological profile have been thoroughly described in our previously published article (6). Generally, 31 (15.19%) patients developed VAP during their ICU stay. Two patients had two episodes of VAP each. *Acinetobacter* was the most common organism (37.83%), followed by *Pseudomonas* and *Klebsiella* species and *E. coli*, while *Elizabethkingia* and *Enterobacter* were the least common organisms. The two isolates of *S. aureus* were the only identified gram-positive organisms.

It was observed that among non-fermenters, colistin and tigecycline were highly active against *A. baumannii*, whereas Tigecycline was active against *Acinetobacter lwoffii*. Piperacillin-tazobactam, gentamicin, and meropenem had good activity against *Pseudomonas* spp. *Elizabethkingia meningoseptica* was only sensitive to ciprofloxacin and tigecycline; All the remaining tested antibiotics were resistant.

Among Enterobacteriaceae, all the isolates of *E. coli* were sensitive to meropenem, and most of them were resistant to beta-lactams; *Klebsiella* was 100% resistant to beta-lactams, and half of the isolates were resistant to meropenem, while *Enterobacter* was completely sensitive to all the tested drugs as reported in Table 2.

All the isolates of *Klebsiella* and *E. coli* representing the ceftazidime zone of ≤22 mm were tested for ESBL production by the phenotypic confirmatory disc diffusion test as shown in the Figures 1 and 2 respectively.

Isolates that yielded a cefoxitin zone diameter of > 18 mm and were resistant to third-generation cephalosporins were tested for AmpC enzyme production by the popular AmpC disk test. Likewise, isolates that were not susceptible to Carbapenems were tested for Carbapenemase production by the mCIM test.

ESBL was confirmed in 40% and 67% of *E. coli and K. pneumoniae*, respectively. Out of 3 Carbapenem-resistant

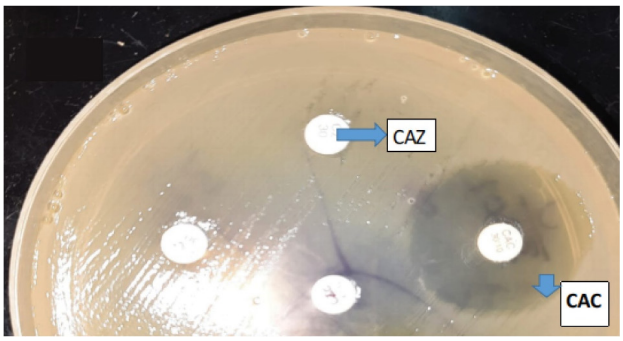

Figure 1. Phenotypic Confirmatory Disc Diffusion Test. Note. *Klebsiella* species showing ESBL production was confirmed by an increase in the zone of ≥ 5 mm for ceftazidime/clavulanic acid (CAC) and cefotaxime/clavulanic acid (CEC) vs. ceftazidime (CAZ) and cefotaxime (CTX) alone, respectively.

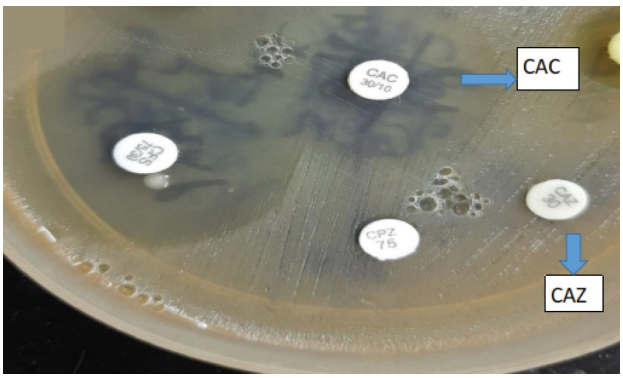

Figure 2. Phenotypic Confirmatory Disc Diffusion Test. Note. ESBL: Extended-spectrum beta-lactamases; *E. coli: Escherichia coli. E. coli* indicating ESBL production was confirmed by an increase in the zone of ≥ 5 mm for ceftazidime/clavulanic acid (CAC) vs. ceftazidime (CAZ) alone. A combination of cefoperazone (CPZ) and cefoperazone sulbactam (CFS) was used as well.

Table 2. Etiological Agents of VAP and Their Antibiotic Resistance Patterns (%)

Etiological Agents (No. of Isolates)	Antibiotic Resistance in % (No. of Isolates)								
1. Non-fermenters	**PTZ**	**GEN**	**CL**	**CIP**	**CPM**	**CAZ**	**MEM**	**TGC**	**SXT**
Acinetobacter baumannii (13)	100 (13)	100 (13)	7.69 (1)	100 (13)	100 (13)	76.9 (10)	100 (13)	15.38 (2)	92.3
Acinetobacter lwoffii (1)	100	100	100	100	100	100	100	0	100
Pseudomonas aeruginosa (8)	50 (4)	25 (2)	37.5 (3)	25 (2)	50 (4)	37.5 (3)	25 (2)	100 (8)	50 (4)
Elizabethkingia meningoseptica (1)	100	100	100	0	100	0	100	0	100
2. Enterobacteriaceae	**AMP**	**GEN**	**AMK**	**CIP**	**CTR**	**CAZ**	**MEM**	**PTZ**	**SXT**
Escherichia coli (5)	100	80	0	100	100	60	0	60	40
Klebsiella pneumoniae (6)	-	100	0	50	100	100	50	100	50
Enterobacter cloacae (1)	0	0	0	0	0	0	0	0	0

Note. PTZ: Piperacillin-tazobactam; GEN: Gentamicin; CL: Colistin; CIP: Ciprofloxacin; CPM: Cefepime; CAZ: Ceftazidime; MEM: Meropenem; TGC: Tigecycline; SXT: Trimethoprim sulfamethoxazole; AMP: Ampicillin; AMK: Amikacin; CTR: Ceftriaxone.

Klebsiella species, only one was a Carbapenemase producer as depicted in the Figure 3.

Isolates demonstrating resistance to carbapenems were selected for the detection of MBL enzymes by IPM EDTA CDT.

Only two of the eight *Pseudomonas* species were tested for MBL (Figure 4) and both were positive, while AmpC β-lactamases were produced by 18% of each of the non-fermenters and Enterobacteriaceae members, respectively.

Based on the results, 50% of the *S. aureus* causing VAP were MRSA as depicted in the Table 3, which was detected by the Cefoxitin 30 microgram disk diffusion method as illustrated in the Figure 5.

Twenty (54%) of the 37 VAP pathogens were MDR in our study as reported in the Table 4, including gram-negative bacteria (Enterobacteriaceae and non-fermenters) producing ESBL, AmpC β lactamases, and MBL (Tables 5 and 6) and gram-positive MRSA.

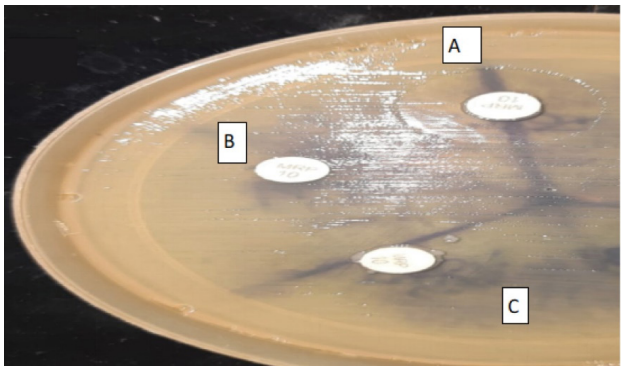

Figure 3. mCIM Results. (A) Negative mCIM - Carbapenemase not detected (Zone diameter>19 mm). (B) Positive mCIM - Carbapenemase detected (Zone diameter- 6 mm). (C) Negative mCIM - Carbapenemase not detected (Zone diameter>19 mm).

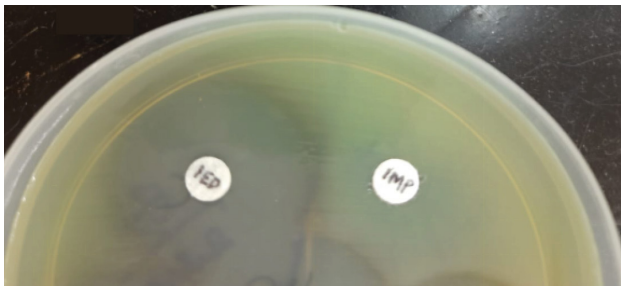

Figure 4. MBL-producing *Pseudomonas aeruginosa*: IMP–EDTA Combined Disc Test Showing an Increased Zone With IMP-EDTA (IED) of 22 mm Compared to Only IMP. Note. MBL: Metallo-beta-lactamases; EDTA: Ethylenediamine tetraacetic acid; IMP: Imipenem.

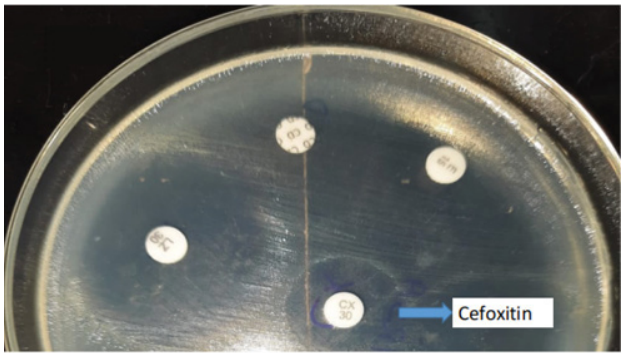

Figure 5. Cefoxitin Disk Diffusion Test: MRSA Positive *Staphylococcus aureus* Species Showing CX (Cefoxitin) Disk Zone>21 mm

Table 3. Etiological Agents (GPC) of VAP the Antibiotic Resistance Pattern (%)

	PEN	CFX	TET	ERY	CIP	CL	VA	LZ	SXT
Staphylococcus aureus (2)	50	50	0	100	100	0	0	0	100

Note. PEN: Penicillin; CFX: Cefoxitin; TET: Tetracycline; ERY: Erythromycin; CIP: Ciprofloxacin; CL: Clindamycin; VAN: Vancomycin; LZ: Linezolid; SXT: Trimethoprim sulfamethoxazole.

Table 4. MDR Pathogens

Organism	Total Isolates	MDR Isolates	Percentage
Non-fermenters	23	10	43.47%
Enterobacteriaceae	12	09	75%
GPC	02	01	50%
Total	37	20	54%

Note. MDR: Multidrug resistance; GPC: Gram-positive cocci.

Discussion

To the best of our knowledge, this is the first study to identify VAP events according to newer NHSN guidelines, including clinical, radiological, and microbiological results rather than only CPIS scoring.

VAP accounts for 1/4th of the infections in critically ill patients and half of the antibiotic prescriptions in mechanically ventilated patients. Several countries have reported mortality rates ranging from 24% to 76%.

A patient seeks medical help only when it is absolutely inevitable owing to limited resources, and by the time, he/she is referred to the tertiary care center, his/her underlying condition is well advanced; this may necessitate a longer duration of mechanical ventilation, which is directly proportional to the development of VAP.

In this study, the most commonly isolated organism was Acinetobacter, followed by *P. aeruginosa*, *E. coli*, and *K. pneumonia*. The organisms implicated in VAP were similar in other studies such as Dube et al (14), Maqbool et al (15), Mathai et al (16), and Ranjan et al (17). *Acinetobacter* indeed has a wonderful ability to grow in various inserted catheters in patients in ICU, particularly the endotracheal tube (18).

In our study, 31% of *Acinetobacter* spp. were AmpC β-lactamase producers, which is less compared to other studies such as Kaur et al. In our study, 66% of *Klebsiella* isolates were ESBL producers, which is similar to the result of Joseph et al (19), whereas it is more when compared to studies by Kaur et al (20) and Sangale et al (21).

MBL producing *Pseudomonas* was 25% in our study, which is less compared to that of Krishnamurthy et al (22), which was 50%, while it is slightly more when compared to the result of Joseph et al (19), which was 20%. Most of the studies showed a similar incidence of MRSA, including Joseph et al (19), Balkhy et al (23), and Sangale et al (21).

MDR *Acinetobacter*, *klebsiella*, and *Pseudomonas* were the common organisms associated with greater mortality, among which *Acinetobacter* (57.14%) had the highest rate

Table 5. ESBL, AmpC β-Lactamase, and Carbapenemase Production Among *Enterobacteriaceae*

Bacterial Isolates	ESBL	AmpC β-Lactamase	Cp-CRE
Escherichia coli (5)	2	1	0
Klebsiella pneumoniae (6)	4	1	1

Note. ESBL: Extended-spectrum beta-lactamases; AmpC: Ampicillin C; Cp-CRE: Carbapenemase-producing carbapenem-resistant Enterobacteriaceae.

Table 6. AmpC β Lactamase and MBL Production Among Non-fermenters

Bacterial Isolates	AmpCβ Lactamase	MBL
Pseudomonas aeruginosa (8)	1	2
Acinetobacter baumannii (13)	4	3
Acinetobacter lwoffii (1)	0	0

Note. MBL: Metallo-beta-lactamase.

in our study, which is correlated with the result of a study from Odisa, where *Acinetobacter* was associated with 80% of mortality. This highlights the need for detecting MDR organisms and treatment rather than giving empirical treatment.

In this study, it was observed that Colistin is highly active against *Acinetobacter* spp., and Piperacillin/tazobactam combination has good activity against *Pseudomonas* spp. These findings need to be further confirmed by large clinical trials since we have only studied less number of isolates in a single tertiary care hospital.

ESBL and AmpC β-lactamases were produced by a large number of the Enterobacteriaceae similar to other studies (19). Therefore, the prophylactic use of antibiotics is not recommended, and exposure to antibiotics is a significant risk factor for colonization and infection with nosocomial multidrug-resistant pathogens as observed by other authors (24).

Conclusion

The notable strength of our study was that it was prospectively conducted with the diagnosis of VAP based on new NHSN guidelines rather than CPIS scoring, which was used earlier. VAP is highly associated with MDR pathogens.

As per our study revealed colistin was good for *Acinetobacter*, Piptaz against *Pseudomonas* species, and *E. coli* to carbapenems compared to *Klebsiella*.

There is a need for a multidisciplinary approach, proper planning, and infection control to combat VAP events, including continuous education and increased awareness of MDR, to reduce the duration of ventilation, to use proper antibiotics only after using susceptibility testing, and to follow all VAP bundles.

Acknowledgements

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Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study was approved by the Research and Ethics Committees of Gandhi Medical College and Hospital, and informed consent was obtained from each patient.

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