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An update on the increasing prevalence of multidrug-resistant pathogens found in mechanically ventilated patients in central India

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Abstract

Background: Rampant and irrational use of antibiotics led to antimicrobial resistance in intensive care units, directly influencing the clinical outcome. The prior introduction of antibiotics, especially broad-spectrum antibiotics, has been identified as a leading cause of hospital-acquired pneumonia. The present study aims to examine the existing scenario of antibiotic resistance due to multidrug-resistant organisms that are detected in mechanically ventilated patients.

Methods: This cross-sectional study was conducted in the department of Microbiology of a tertiary care hospital in Central India. A total of 410 endotracheal secretions were collected. The endotracheal aspirate of adult patients admitted to the medicine intensive care unit and on mechanical ventilation was received at the microbiology laboratory for processing by standard bacteriological techniques. Drug susceptibility testing was done using the Kirby-Bauer disc diffusion method according to the indications mentioned in Clinical and Laboratory Standards Institute 2021.

Results: Out of 410 collected endotracheal secretion samples, 332 (81 %) samples demonstrated bacterial growth. A total of 265 (80%) cases fulfilled the inclusion criteria. From 265 samples, 92 (34.7 %) patients were clinically and microbiologically confirmed as cases of ventilator-associated pneumonia. Over eighty percent of gram-negative bacilli were multidrug-resistant strains *(Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa).*

Conclusion: Real understanding of multidrug-resistant pathogens, early isolation as well as avoiding long-term antibiotic intake can reduce mortality levels currently linked with late-onset ventilator-associated pneumonia.

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Introduction

Mechanical ventilation is a life-restoring approach, still, it is still responsible for acquiring respiratory infections, causing maximum mortality in critical patients (1). Ventilator-associated pneumonia (VAP) depicts infection of the lung parenchyma acquired by the invading pathogens, attained post-ventilation (2). Intensive care unit (ICU) infection is an autonomous foreteller for bad outcomes, and VAP caused by multidrug-resistant (MDR) strains is hard to cure (3). The human microbiome has been known as a pool of antibiotic-resistance genes. Bacteria use a genetic mechanism to resist antibiotic effect via gene mutations linked with antibiotic action and acquire resistant genes via horizontal transfer such as transformation, transduction, and conjugation of plasmids or transposons (4). *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii*, *Pseudomonas aeruginosa, and Enterobacter spp.* are known as the "ESKAPE" group of pathogens that have developed multidrug resistance property (5). These bacteria are mainly responsible for life-threatening nosocomial infections in mechanically ventilated patients, characterized by probable drug-resistant procedures (5).

The incidence of MDR isolates differs between healthcare centers and among different patient groups, as a part of patients with complicated infections are expected to have an enormous amount of drug resistance (6). Moreover, comprehending the role of antimicrobial resistance related to VAP is critical in this century of ceaseless progression of resistant clones that pose a dire hazard to universal health (7). Therefore, the present study aims to determine the existing scenario of MDR strains arising in mechanically ventilated patients. This study also aims to screen the presence of β-lactamase producers among the isolates; subsequently, the organisms isolated from endotracheal aspirate causing VAP will be identified.

Methods

This cross-sectional study was conducted for 1.5 years, from May 2021 to October 2022, at the Department of Microbiology, GMCH, Nagpur, after obtaining due approval from our institutional ethics committee with registration number 1444. Patient consent was obtained before the investigation by the hospital administration. The researchers confirm that the present study complies with all the regulations. Clinical trials in the present study were not applicable. The following were the inclusion criteria of the patients taken for this study: (i) The age of the patients was greater than 18 years, (ii) Patients who underwent mechanical ventilation for more than 48 hours, and (iii) Patients fulfilling the radiological and clinical parameters. The radiological and clinical conditions include the existence of any recent or ongoing lung infiltrate, in addition to any two of these traits, including fever more than 38°C, high or low white blood cell count, and purulent lower pulmonary secretions (8).

The present study consisted of all adult patients on mechanical ventilation admitted to the medicine intensive care unit of a tertiary care hospital in central India. A total of 410 endotracheal secretions were collected. The endotracheal aspirate of patients was immediately inoculated and streaked onto nutrient agar, 5 % sheep blood agar, and MacConkey agar (HiMedia Laboratories Pvt. Limited, Mumbai, India). Agar plates were incubated under aerobic conditions at 37°C for 24 hours. Isolated strains were processed and distinguished as per the standard bacteriological procedures, and pathogens were identified based on the results of biochemical test (9).

Antimicrobial susceptibility testing was done using the Kirby-Bauer disc diffusion method (10). Drugs used in the testing were as per recommendations mentioned in Clinical and Laboratory Standards Institute 2021 (11). Each gram-negative isolate was further subjected to extended-spectrum ß-lactamases (ESBL), AmpC (Cephalosporinases), and metallo-beta-lactamase (MBL) production for detection of β-lactamase producers. Furthermore, the gram-positive organisms were tested for methicillin-resistant *Staphylococcus* aureus and inducible clindamycin resistance. The tests conducted for gram-negative isolates were as follows:

i) **ESBL:** Based on the combined disk diffusion method, the test organism was inoculated on a Muller Hinton agar plate in the presence of ceftazidime (30µg) disc alone and with clavulanic acid disc (30/10µg). The discs were arranged on the plate and incubated for 24 hours at 37°C. If the strain showed the zone of inhibition of ceftazidime plus clavulanic acid disc, more than or equal to 5 mm that of ceftazidime disc alone, then the organism was described as ESBL producer (11).

ii) **AmpC:** Based on the disc antagonism method, the test organism was inoculated on Muller Hinton agar plate in the presence of any of the combination of Cefotaxime (30 µg) and cefoxitin (30 µg) discs or ceftazidime (30 µg) and imipenem (10 µg) discs. The discs were placed 20 mm apart from the center on the plate and incubated at 37°C for 16-18 hours. Isolates showing "blunting" of the cefotaxime zone of inhibition adjacent to the cefoxitin disc or "blunting" of the ceftazidime zone of inhibition beside the imipenem disc were described as inducible AmpC-producing organism (12).

iii) **MBL:** Based on the disc potentiation method, the test organism was inoculated on Muller Hinton agar plate, and two imipenem discs (10µg) were placed at a distance of 20 mm from each other. 5µl of 0.5M (750µg) ethylenediamine tetra acetic acid was dispensed on one disc. The plate was incubated at 35°C for 16-20 hours. When the zone diameter of the antimicrobial

drugs tested in conjugation with ethylenediamine tetra-acetic acid was greater than or equal to 5 mm of that of the zone diameter when antimicrobial drugs were tested alone, the organism was confirmed as MBL-producing (13).

The following were the tests conducted for gram-positive isolates:

i) **Test for detection of methicillin-resistant staphylococcus aureus:** cefoxitin disc diffusion method: 30µg of cefoxitin disc was placed on the Muller Hinton agar plate inoculated with the test organism. The plate was incubated at 34°C±1°C aerobically for 16 to 18 hours. The test was reported to be positive if the zone of inhibition of cefoxitin is less than or equal to 21 mm; otherwise, it is negative.

ii) **Test for detection of inducible clindamycin resistance:** 15 µg of Erythromycin and 2 µg of Clindamycin discs were placed 15 to 26 mm apart. These discs were incubated at 35°C±2°C aerobically for 16 to 18 hours. The test was considered positive if the flat zone (D-shaped zone) of inhibition of clindamycin was observed; in contrast, it was considered negative if hazy growth around clindamycin within the zone of inhibition was observed, even with the appearance of a D-shaped zone.

The inhibition zones were measured, and the organisms were reported as sensitive or resistant to the antimicrobial agent tested according to Clinical Laboratory Standard Institute 2021 guidelines. The standard American Type Culture Collection strain numbers 25923, 25922, 27853, 13883, and 12457 were used for comparison *of Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii*, respectively, for quality control.

Results

VAP reflects an actual public health issue due to its extended duration of mechanical ventilation in the ICU, which incurs additional expense with an increased chance of morbidity, and, therefore, antibiotics are used in mechanically ventilated patients (14). Usually, the mortality rate ranges between 24 and 50 % under normal VAP cases; however, the mortality rate rises to 76 % in VAP cases with MDR strains (15). Minimizing pathogen circulation and antibiotic resistance patterns results in better antibiotic treatment and care of the patients (16).

410 endotracheal secretions were received and processed in the microbiology laboratory using standard conventional methods. Out of a total of 410 endotracheal secretions, 332 (81 %) samples showed the presence of bacterial growth. These endotracheal secretions showing growth were further investigated for the symptoms of VAP. Of these 332 samples, 265 (80 %) cases fulfilled the inclusion criteria. 92 (34.7 %) out of 265 samples were confirmed as VAP clinically and microbiologically. The present study reflects the pathogens isolated from VAP primarily A. *baumannii* (35.6 %) and K. *pneumoniae* (26 %). Table 1 shows antibiotic resistance pattern for the gram-negative bacilli, depicting maximum resistance against most of the antibiotics (90-100%). Table 2 demonstrate maximum MDR strains in A. *baumannii* and K. *pneumoniae* (91%). Table 3 indicates the distribution of β-Lactamases namely ESBL, AmpC and MBL in endotracheal aspirates of VAP cases among MDR isolates.

Table 1. Antibiotic resistance pattern for the gram-negative bacilli recovered from VAP cases

No.	Antibiotics	*A. baumannii* (N = 47)	*P. aeruginosa* (N = 25)	*A. lwoffii* (N = 10)	*K. pneumoniae* (N = 34)	*E. coli* (N = 9)	*C. koseri* (N = 3)	*P. mirabilis* (N = 2)
		Number of samples resistant to antibiotic (n), Resistant pattern (n/N) (%)						
1	Gentamicin	45 (96)	18 (72)	10 (100)	27 (78)	5 (55)	3 (100)	1 (50)
2	Tobramycin	45 (96)	25 (100)	10 (100)	34 (100)	7 (77)	2 (66)	2 (100)
3	Levofloxacin	46 (98)	24 (96)	10 (100)	33 (97)	9 (100)	3 (100)	2 (100)
4	Amikacin	45 (96)	23 (92)	10 (100)	34 (100)	9 (100)	2 (66)	1 (50)
5	Cefepime	47 (100)	25 (100)	10 (100)	32 (94)	8 (89)	2 (66)	1 (50)
6	Piperacillin-tazobactam	46 (98)	23 (92)	9 (90)	33 (97)	8(89)	3 (100)	1 (50)
7	Ceftazidime	47 (100)	16 (64)	10 (100)	-	-	-	-
8	Aztreonam	-	21 (84)	-	-	-	-	-
9	Meropenem	42 (88)	16 (64)	7 (70)	30 (88)	8 (89)	2 (66)	1 (50)
10	Netilmicin	-	13 (52)	-	-	-	-	-
11	Amp-sulbactam	45 (96)	-	10 (100)	-	-	-	-
12	Minocycline	46 (98)	-	9 (90)	-	-	-	-
13	Cotrimoxazole	44 (93)	-	6 (60)	31 (91)	6 (66)	1 (33)	2 (100)
14	Amoxycillin-clavulanate	-	-	-	34(100)	8 (89)	3 (100)	2 (100)
15	Ampicillin	-	-	-	34 (100)	9 (100)	3 (100)	2 (100)
16	Cefazolin	-	-	-	32 (94)	9 (100)	3 (100)	2 (100)
17	Cefuroxime	-	-	-	32 (94)	8 (89)	3 (100)	2 (100)
18	Cefoxitin	-	-	-	31 (91)	8 (89)	3 (100)	1 (50)
19	Cefotaxime	-	-	-	32 (94)	8 (89)	3 (100)	1 (50)
20	Ertapenem	-	-	-	31 (91)	8 (89)	2 (66)	1 (50)

Table 2. MDR among pathogens isolated from VAP cases

No.	MDR pathogens	Total number of MDR organisms (N)	Total number of MDR organisms (%)
1	*Acinetobacter baumannii*	47	43 (91)
2	Klebsiella pneumoniae	34	31 (91)
3	Pseudomonas aeruginosa	25	22 (88)
4	Acinetobacter lwoffii	10	8 (80)
5	Escherichia coli	09	7 (77)
6	Citrobacter koseri	03	1 (33)
7	Proteus mirabilis	02	2 (100)

Table 3. Distribution of various β-Lactamases in endotracheal aspirates of VAP cases

No	Pathogens	Total MDR isolates	ESBL (%)	AmpC (%)	MBL (%)
1	K. pneumoniae	34	15 (44)	8 (23.5)	-
2	E. coli	9	03 (33)	-	-
3	A. baumannii	47	-	12 (25.5)	21 (44.6)
4	P. aeruginosa	25	-	-	10 (40)

Discussion

The present study showed that the pathogens isolated from VAP were gram-negative bacilli, predominantly *A. baumannii* (35.6 %), *K. pneumoniae* (26 %), and *P. aeruginosa* (19 %), followed by 7 % of *A. lwoffii* and *E. coli* while *Proteus mirabilis* and *Citrobacter koseri* were found in traces (1-2 %). Koirala *et al.* (2010) reported the dominance of gram-negative organisms (40.3%), namely *P. aeruginosa*, *E. coli, Klebsiella spp.*, and *Enterobacter cloacae* in tracheal aspirates of 50 patients with fever more than 38°C (17). Tullu *et al.* (1998) reported the presence of *E. coli* (33.33%), *Klebsiella spp.* (29.16%), and *Pseudomonas spp.* (11.46%) as gram-negative organisms from 70 endotracheal tube tips of patients (18). Nonetheless, *S. aureus* (23.6%) was the gram-positive organism predominant in the study by Amini *et al.* (2009). Further, the authors also reported the presence of gram-negative organisms (*Klebsiella spp.* (23.3%) and *Acinetobacter spp.* (20.7%)) in the patient's tracheal tubes in ICU (19).

Table 1 shows non-fermenters' resistance (*A. baumannii*, *P. aeruginosa*, and *A. lwoffii*) against different antibiotics. From Table 1, it can be observed that *A. baumannii* exhibited more than 95 % resistance against all antibiotics except amikacin. In 2010, Joseph *et al.* reported 43%, 57%, and 86 % resistance against piperacillin-tazobactam, meropenem, and amikacin, respectively, for *A. baumannii*, isolated during late-onset VAP (20). Apart from these drugs, the resistance shown against *A. baumannii* was 100 %. Further, *P. aeruginosa* showed more than 92 % resistance against tobramycin, levofloxacin, amikacin, cefepime, and piperacillin-tazobactam. Moreover, *P. aeruginosa* showed 84%, 72%, 64%, and 64% resistance against aztreonam, gentamicin, ceftazidime, and meropenem, respectively. In a study by Goel *et al.*, out of 57 isolates of *P. aeruginosa*, a high rate of resistance was shown towards aztreonam (94.7%), netilmicin (70.2%), and ceftazidime (68.4%). In comparison, 23 isolates (40%) were resistant to all the other antibiotics used against *P. aeruginosa*. Meropenem was the most effective (77.2%) drug in vitro, followed by the combination of piperacillin-tazobactam (50.5%) in their study (21)**.** According to a multicentre longitudinal surveillance program, piperacillin-tazobactam and meropenem were the most effective agents against *P. aeruginosa*, showing resistance of only 20% (22). These findings suggest that meropenem should be used cautiously in ventilated patients to prevent the development of resistance by microorganisms against this drug. It can be predicted that *Pseudomonas* species show higher levels of antibiotic resistance due to the presence of different types of enzymes (*β*-lactamases and aminoglycoside-modifying enzymes), the loss of porin proteins and the presence of efflux pumps (23).

Table 1 shows the resistance of Enterobacterales (*K. pneumoniae*, *E. coli*, *C. koseri*, and *P. mirabilis*) against different antibiotics. From Table 1, it can be observed that *K. pneumoniae* generated more than 90% resistance against all the antibiotics except gentamicin. Such elevated levels of resistance shown by *K. pneumoniae* are attributed to the production of ESBL, AmpC, and MBL, along with the efflux of the drug (23). In a case study reported by Dey et al. (2007), 80 % of *E. coli* and 100 % of *K. pneumoniae* were ESBL producers; therefore, the authors marked these organisms as MDR (24).

Table 2 shows that the maximum number of MDR pathogens in VAP cases was observed in *A. baumannii* (91 %) and *K. pneumoniae* (91 %), followed by *P. aeruginosa* (88 %), *A. lwoffii* (80 %), and *E. coli* (77 %). Traces of *C. koseri* and *P. mirabilis* were also found in VAP. A previous study by Kumari *et al.* (2002) reported the findings from 489 bacterial isolates cultured from lower respiratory tract secretions (Tracheal or bronchoscopy aspirates) of 270 patients in ICU. The authors declared *A. baumannii* (6.6 %), *P. aeruginosa* (5 %), and *Klebsiella* species (1.7 %) as MDR pathogens (25). Furthermore, a study conducted in 2018 reported that 54% *K. pneumoniae*, 60% *A. baumannii,* and 19% *P. aeruginosa* were MDR strains. The study was conducted on 94 respiratory samples obtained from bronchoalveolar lavage (BAL) and endotracheal aspirate (ETA) (26).

In the present study, the high resistance (91 %) shown by *A. baumannii* against the antibiotics can be attributed to several factors, such as the potential to persist in surrounding and human reservoirs because of less nutritional demand to grow at distinct temperatures and pH, which favor the acquisition of MDR characteristics in *A. baumannii*. Vila et al. also noted the above observation (27). Further, this study showed that *K. pneumoniae* had the second highest population of pathogens, which undergoes horizontal transfer of drug-resistant genes through mobile genetic elements that facilitate the production of ESBL and other resistant mechanisms, ultimately aiding the survival of *K. pneumoniae* in hospitalized patients. Hence, it acquires the MDR characteristics. Ashwath *et al.* (28) had similar observations regarding *K. pneumoniae*. *P. aeruginosa* exhibited MDR properties in the present study and showed a resistance of 88 % against antibiotics, which can be attributed to its innate potential to acquire both inherent and acquired antibiotic resistance from the adjoining bacteria in the surroundings and its capacity to carry multi-resistance plasmids (29). Wagner et al. also described this observation (30). Therefore, it can be concluded that the antibiotic resistance shown by pathogens (*A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*) marked in this study has increased. The rapid emergence of antibiotic-resistant microbes in the ICU could be detrimental to VAP patients.

Table 3 shows that 44 % *K. pneumoniae* and 33 % *E. coli* were identified as ESBL producers. Extensive testing of third-generation cephalosporins can be described as a cause for the increase in ESBL producers in India (31). Gram-negative bacteria produce ESBLs that generate resistance against extended-spectrum cephalosporins, aztreonam, narrow-spectrum cephalosporins and anti-gram-negative bacterium penicillins (32). Hirakata *et al.* (33) identified 11% to 14% of *E.coli* and *Klebsiella* species as ESBL producers. A study conducted in Nepal (34) showed a higher prevalence of *E. coli* at 80% and *K. pneumoniae* at 57.1%, in contrast to the present study.

Table 3 indicates that 25.5% of *A. baumannii* and 23.5% of *K. pneumoniae* were identified as AmpC producers. It can be observed that the above organisms produce plasmid-mediated AmpC β-lactamases; hence, they confer resistance to 7-α-methoxy-cephalosporins (Cefoxitin) and β-lactamase inhibitors (Ampicillin-sulbactam, amoxicillin-clavulanate, and piperacillin-tazobactam). Therefore, these organisms pose new threats to VAP patients. The above observations were also marked by Philippon *et al.* (35). A study conducted by Golia *et al.* (36) demonstrated that none of the gram-negative organisms were AmpC producers when the total number of endotracheal aspirate samples was 52. NG *et al.* (37) examined 98 samples of tracheal aspirates, in which 11 samples were identified as *A. baumannii* and 19 were identified as *K. pneumoniae*. Among *A. baumannii* samples, 9.09 % of isolates were AmpC producers, whereas 10.52 % of isolates of K. pneumoniae samples were AmpC producers.

Table 3 shows that 44.6 % of *A. baumannii* and 40 % of *P. aeruginosa* were identified as MBL producers. From the current study, it can be inferred that the gram-negative bacteria producing MBLs can become resistant to carbapenem (Ertapenem and meropenem), making VAP patients difficult to treat. Nordmann *et al.* (38) reported the above observation in their study. In 2003, a study by Lee *et al.* (39) reported that MBL production was observed only in 14.2% of *A. baumannii* and 11.4% of *P. aeruginosa*. In contrast to the present findings, a previous study in 2015 reported no MBL producers among 11 *Acinetobacter spp.* (37) and observed 2 (29%) out of 7 *P. aeruginosa* (40).

Conclusion

The research presented in this paper focused on identifying potential microorganisms as entrants to the multi-drug resistant category. Ventilator-associated pneumonia remains a common challenge for critical patients, leading to significant morbidity, antibiotic use, and costs. The present study presented two important microbiological complications in tracheostomized patients. The first is a high growth rate, and the second is the predominance of multi-drug resistant pathogens, which may be attributed either to selective decontamination of the digestive tract with different antibiotics or empirical use of broad-spectrum antibiotics and non-adherence to hospital antimicrobial position.

A peculiar finding of the present study was that out of 410 endotracheal secretion samples, 80% fulfilled the inclusion criteria, and 34.7% were confirmed to be ventilated-associated pneumonia. Among them, gram-negative strains were also isolated, amongst which the most predominant microorganism was *A. baumannii* (35.6 %), followed by *K. pneumoniae* (26 %) and *P. aeruginosa* (19 %). Among the VAP strains, 80% were multi-drug resistant owing to the production of β-lactamase such as ESBL (42%), AmpC (24.6%), and MBL (43%), reflecting high resistance rates to common antibiotics such as cephalosporins, carbapenems, aminoglycosides and β-lactam/β-lactamase inhibitor combinations, which are typical and potent drugs for hospital infections leading to high mortality rate.

Recommendation

Making changes to antibiotic prescribing patterns, such as alterations and rotations, could help reduce antibiotic resistance. Moreover, vigilant supervision, laboratory testing of drugs before starting antimicrobial therapy, and implementing a restricted antibiotic policy may improve the management of multidrug-resistant (MDR) pathogens. This can help prevent a scenario similar to the post-antibiotic era, where even common infections may become untreatable, leading to countless deaths.

List of abbreviations

VAP: Ventilator-Associated Pneumonia, ICU: Intensive Care Unit, MDR: Multi-Drug-Resistant, ESBL: Extended-Spectrum *β*-Lactamase, MBL: Metallo-*β*-Lactamases

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Ethical statement

Ethical number was obtained after receiving due approval from our institutional ethics committee with registration number 1444.

Conflicts of interest

On behalf of all the authors, the corresponding author states that there is no conflict of interest.

Author contributions

Sonakshi Dwivedi: Conceptualization, methodology, data collection, investigation, visualization, writing-original draft, review and editing. Vaishali Rahangdale: Conceptualization and design and data analysis. Swati Bhise: reviewing the initial draft and managing resources. Sunanda Zodpey: project administration and supervising the project. All the authors have critically reviewed and approved the final draft and are responsible for the manuscript's content.

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