Colistin resistance in organisms causing ventilator-associated pneumonia - Are we going into pre-antibiotic era?

Sonika Agarwal, Barnali Kakati, Nand Kishore, Sushant Khanduri, Mukta Singh

Abstract

***Introduction*: Ventilator-associated pneumonia (VAP) is one of the most common infections in mechanically ventilated patients. VAP is usually caused by multidrug resistant bacteria. The beta-lactam antibiotics, which were once considered the backbone of antibiotic therapy is under strain due to a variety of bacterial antibiotic resistance. Recent evidence suggests that colistin is the only cannon left in the medical armory to treat bacterial infections, mainly those acquired in the hospital that no other drug can treat. But excessive use of colistin has recently led to resistance to these group of drugs. Initially, resistance to colistin was due to mutations but recently detected plasmid-mediated colistin resistance, which is transferrable, heralds the breach of the last group of antibiotics, polymixins. Colistin resistance is on the rise, especially in South East Asia countries. So strict infection control policies are required to control the spread of this infection.**

***Objective*: This study was conducted to see the burden of colistin resistant organisms causing VAP in ICU of Himalayan Institute of Medical Sciences, Dehradun, India.**

***Design*: A prospective observational study.**

***Setting*: Study was conducted in a 40-bed semi-closed ICU of a tertiary care super specialized hospital between August 2016 to April 2017.**

***Patients and participants*: Out of 2304 patients admitted to ICU 420 had a suspicion of VAP. A total of 476 lower respiratory tract samples were collected from 400 patients with clinical evidence of lower respiratory tract infections in form of endotracheal (ET) aspirate, tracheal tube (TT) aspirate, and bronchoalveolar lavage (BAL) specimens.**

***Intervention*: Organism identification and the susceptibility testing were done by using an automated system VITEK 2.**

***Result*: Out of 476 sample received, only 186 samples organisms were isolated, which showed Acinetobacter baumanii was the most common organism. It was found that 19 organisms had resistance to colistin. Klebsiella pneumoniae (25.7%) was the most common organism, which was resistant to colistin, followed by Pseudomonas aeruginosa (16%) and Acinetobacter baumanii (2.4%).**

***Conclusion*: The emergence of colistin resistant strains is a very serious problem as there are only few treatment options. As colistin use is a risk factor for colistin resistance, colistin should not be used alone, combination therapy should be preferred.**

Key words: Ventillator-associated pneumonia, colistin, antibiotic resistance.

Introduction

Pneumonia that occurs 48-72 hours or more following endotracheal intubation is defined as ventilator-associated pneumonia (VAP). (1) VAP contributes to approximately half of all cases of hospital-acquired pneumonia and it is the second most common nosocomial infection in the intensive care unit (ICU). (2) VAP is usually caused by multidrug resistant bacteria, with no difference of early or late onset VAP. (3) Carbapenems, which was once considered as a backbone of therapy for multidrug-resistant (MDR) infections, appears to be broken beyond repair. (4) Unavailablity of newer antibiotics led to the revival of polymyxin group of antibiotics, which have adverse effects. (5) Polymyxins are now considered as the last resort for treatment of infections with carbapenem-resistant Gram-negative bacteria. However, due to selection pressure of overuse of colistin, resistance to these compounds has begun to emerge. (6,7) Recently discovered plasmid mediated colistin resistance and clonal expansion through horizontal transmission is of great concern. (8) The present study was aimed to see the burden of colistin resistant organ-

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organisms causing VAP in ICU of a tertiary care hospital.

Material and methods

The prospective observational study was conducted from August 2016 to April 2017 in ICU of Himalayan Institute of Medical Sciences, Dehradun. Institutional research and ethical committee clearance for the study was taken. Patients who were intubated or mechanically ventilated for ≥48 hrs with new evidence of lower respiratory infections were included in the study. For all patients, personal profile information was recorded and acute physiology and chronic health evaluation (APACHE) II severity scoring was calculated at the time of admission. Patients were monitored in ICU till they were shifted out of ICU. Diagnosis of VAP was made by ICU consultants and clinical pulmonary infection score (CPIS) ≥6 was calculated to confirm the diagnosis. (1,9) The samples of suspected VAP patients were collected in a sterile container with aseptic techniques and sent to the microbiology lab. The lower respiratory clinical specimens received in Microbiology Department from ICU included endotracheal aspirate, tracheal tube aspirate, and bronchoalveolar lavage. After confirming the quality, the samples were plated on sheep blood agar (SBA), chocolate agar (CA), and Mac Conkey agar (MA) and were incubated overnight at 37^{o}C for 48 hrs at 5% CO2 incubator. Lower the threshold for quantitative cultures was considered as 10^5 CFU/ml. Organisms were identified and antimicrobial susceptibility tests were done by using an automated system VITEK 2 for amikacin, amoxicillin-clavulanic acid, aztreonam, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, tobramycin, trimethoprim-sulfamethoxazole, colistin for Gram-negative organisms, and for clindamycin, linezolid, vancomycin and teicoplanin for Gram-positive organisms. Quality control strains were used Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus ATCC 25923, and E. coli ATCC 25922. The result of susceptibility testing was interpreted as per CLSI 2015 guidelines. (10) Colistin resistant strains were defined as MIC≥4. (10,11)

Result

Total of 2304 patients were admitted to ICU from Aug 2016 to April 2017, where 400 patients were suspected to develop VAP. After microbiology testing only 186 were found positive to have VAP. Antimicrobial susceptibility of these organisms was tested. The demographic characteristics and other findings are described in **Figure 1**. Baseline characteristics of confirmed VAP cases are summarized in **Table 1**. VAP was seen more common in males and in elderly especially in 61-70 years with multiple co-morbidities. Most common organisms isolated were Acinetobacter baumanii followed by Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterobacter aeruginosa, Staphylococcus species, and others as showed in **Figure 2**. Most common colistin resistant isolated bacteria were Klebsiella pneumoniae followed by Pseudomonas aeruginosa, and then Acinetobacter baumanii. Other bacteria, which were found to be colistin resistant included 2 Proteus species and 1 Serratia, which were intrinsically resistant to colistin (**Table 2**).

There was no significant difference in the outcome of VAP patients with colistin resistant and colistin sensitive strains as summarized in **Table 3**.

Discussion

Antibiotic resistance is usually a slow-moving crisis. The emergence of multi and pan-drug-resistant Gram-negative bacteria and the lack of new antibiotics to combat them has led to the revival of polymyxins. (5,12) Polymyxins, a group of polypeptide antibiotics was discovered in the 1950s. However, because of the reported high incidence of nephrotoxicity, the intravenous formulations of colistin and polymyxin B were gradually abandoned in most parts of the world in the early 1980s. Colistin targets the bacterial cell membrane and causes its disruption. (13) Colistin is considered as a last resort antibiotic in carbapenem-resistant Gram-negative infections. But rise in carbapenem resistance leading to overuse and inappropriate use of colistin has resulted in the emergence of colistin resistance. (14)

Colistin resistance develops due to chromosomally mediated modulation of two-component regulatory systems leading to modification of lipid. (15) Activation of lipopolysaccharide-modifying genes are involved in polymyxin resistance in Gram-negative bacteria. The recently reported plasmid mediated colistin resistance, which is easily transferrable, will seriously limit the lifespan of the polymyxins as the backbone of regimens against multiple resistant Gram-negative bacilli. (16)

Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae readily develop multiple resistance mechanisms to various classes of antibiotics. (17,18) In our study also these organisms were the most common to develop resistance against colistin. In addition, they are im-

portant nosocomial pathogens and are responsible for a considerable proportion of infections in patients in Intensive Care Units (ICUs) worldwide. Hence, infections by MDR P. aeruginosa, A. baumannii, and K. pneumoniae strains have become common in healthcare institutions. The current scenario is that the continuously evolving the resistance of P. aeruginosa, A. baumannii, and K. pneumoniae to antibiotics has led to the emergence of clinical isolates susceptible to only one class of antimicrobial agents and eventually to pan-drug-resistant (PDR) isolates, i.e. resistant to all available antibiotics. (19)

Klebsiella pneumoniae, a rod-shaped Gram-negative bacterium, is an important pathogen in the community- and hospital-acquired infections. Klebsiella pneumoniae that produce K. pneumoniae carbapenemase (KPC) has rapidly spread across hospitals worldwide in the past decade. (20) Colistin remains the first line treatment for these infections. With the rise in colistin usage, cases of colistin resistant Klebsiella pneumoniae carbapenemase (KPC)-producing strains are reported globally. (21) Colistin resistance has been reported during treatment. (22,23) This emergence of colistin resistance (ColR) in carbapenem resistant, K. pneumoniae creates a therapeutic the challenge that threatens us to return to a "pre-antibiotic era". (24)

In present study maximum, colistin resistance was seen in Klebsiella pneumoniae, which was 25%, which was same as seen by Ghafur, et al from India. (25) There lies a concern for transmission of colistin resistant K. pneumoniae within the hospital and several outbreaks of infections have been reported. (26) Colistin resistant isolated K. pneumoniae strains were reported in Greece at 10.5-20% (27,28) followed by South Korea (6.8%), (29) Singapore (6.3%), (30) and Canada (2.9%). (31) Colistin resistance was found to be independently associated with poor prognosis in case of Carbapenem resistant Klebsiella. (32)

P. aeruginosa is one of the major causes of hospital-acquired infections and is responsible for about 10-20% of nosocomial infections in patients admitted to the Intensive Care Units (ICUs). Prolonged use of carbapenem and colistin has resulted in a development of colistin resistance. (33) In our study colistin resistant, Pseudomonas is reported to be 16%, which was high as compared to another study from North India by Wattal, et al (34) which showed 8% resistance. Satyajeet, et al showed that Pseudomonas shows maximum colistin resistance among Gram-negative bacteria. (35) These study included all sites infections while our study included only VAP.

Treatment with colistin and its duration is a major risk factor for the emergence of colistin resistance. It is also associated with the rise of infections with other multi-drug resistant Gram-negative organisms, which are intrinsically resistant to colistin such as Proteus, Providencia and Morganella. (28) In our study also 3 other bacteria found to be colistin resistant included 2 proteus and 1 Serratia, which are intrinsically resistant to colistin. Another matter for concern is the parallel development of colistin resistance in Acinetobacter baumannii, a possible co-infecting or co-colonising organism found mainly in ICU patients and other critically ill patients. (36) In our study, colistin resistance in Acinetobacter was low about 2.4% though we were not able to detect heteroresistance. Colistin heteroresistance is defined as bacteria with colistin MIC of 2 mg/L in which some detectable subpopulations were able to grow in the presence of >2 mg/L colistin. (37) In other studies Asia shows maximum colistin resistance while Europe and North and South America the rate of colistin resistance in A. baumannii has generally been below 7%. (38-41) However, in studies conducted in Bulgaria, (42) Spain, (43) and Turkey (44-46) rates of colistin resistance in A. baumannii was 16.7%, 19.1%, and between 1-4%, respectively. In our study colistin resistance was not associated with increased mortality but length of stay was slightly increased as compared to colistin sensitive groups, which were same as Matthaiou's study in which there was no significant difference in mortality between the group infected and/or colonized with colistin resistant and colistin susceptible microorganisms. (47)

Conclusion

Colistin forms the backbone of antibiotic therapy for MDR infections in the 21st century but colistin resistance has started emerging. Extensive use of colistin for the treatment of MDR infections have led to the development of colistin resistance. Multiple co-morbidities, invasive procedures, ICU length of stay, and most important colistin exposure are the major driving factors for colistin resistance. Selection pressure of increased use of colistin has not only increased colistin resistance but also has increased the infections with bacteria, which are intrinsically resistant to colistin. Recently plasmid mediated colistin resistance, which is easily transferrable is of great concern. So, to control this trend, a multidisciplinary approach including implementation of strict infection control measures, antibiotic stewardship, and widespread promotion of better awareness of the danger of

antimicrobial resistance is crucial to preserving the last therapeutic options for infections with multi-drug-resistant Gram-negative bacteria. Further work is required for the possible synergistic effects of antimicrobial combinations for the treatment of multi- and pan-drug resistant infections to save us from entering into the pre-antibiotic era.

Table 1. Baseline characteristic of diagnosed VAP cases

	n=186
Age	
- Median (yrs)	56
- Range (yrs)	12-96
Age group (n, %)	
- 10-20	11 (5.9)
- 21-30	23 (12.36)
- 31-40	16 (8.6)
- 41-50	31 (16.66)
- 51-60	32 (17.2)
- 61-70	52 (27.95)
- >70	21 (11.29)
Gender (n, %)	
- Male	129 (69.36)
- Female	57 (30.64)
APACHE II score (mean)	23
Cause of admission to ICU	
- Chest disease	18 (9.7)
- Neuromedicine	40 (21.5)
- Head injury	41 (22)
- Sepsis with MODS	61 (32.8)
- CKD	3 (1.6)
- CLD	12 (6.45)
- CAD	3 (1.6)
- Acute pancreatitis	4 (2.1)
- Poisoning	4 (2.1)

Legend: VAP=ventilator-associated pneumonia; APACHE II=Acute physiology and chronic health evaluation II; MODS=multiorgan dysfunction syndrome; CKD=chronic kidney disease; CLD=chronic liver disease; CAD=coronary artery disease.

Table 2. Organisms isolated from the sample of patients with VAP and frequency of colistin resistance

Organisms isolated	Frequency (n, %)	Colistin resistant (n, %)
Acinetobacter baumanii	83 (44.6)	2 (2.4)
Pseudomonas aeruginosa	31 (16.7)	5 (16)
Klebsiella pneumoniae	32 (17.2)	8 (25)
Escherichia coli	16 (8.6)	0 (0)
Enterobacter aeruginosa	7 (3.7)	1 (14.2)
Staphylococcus species	5 (2.6)	5 (100)
Others	12 (6.5)	3 (25)*

Legend: VAP=ventilator-associated pneumonia; *=including 2 Proteus species and 1 Serratia

Table 3. Outcome of patients with colistin resistant Gram-negative organisms causing VAP

	Colistin resistant organisms	Colistin sensitive organisms
No. of days on ventilator (mean, days)	11.33	10.02
ICU length of stay (mean, days)	13	12.12
Outcome of patients - Expired - LAMA - Discharge	 3 (15.8) 3 (15.8) 13 (68.4)	 44 (26.3) 38 (22.75) 85 (50.89)

Legend: VAP=ventilator-associated pneumonia; ICU=intensive care unit; LAMA=left against medical advice

Figure 1. Patient samples

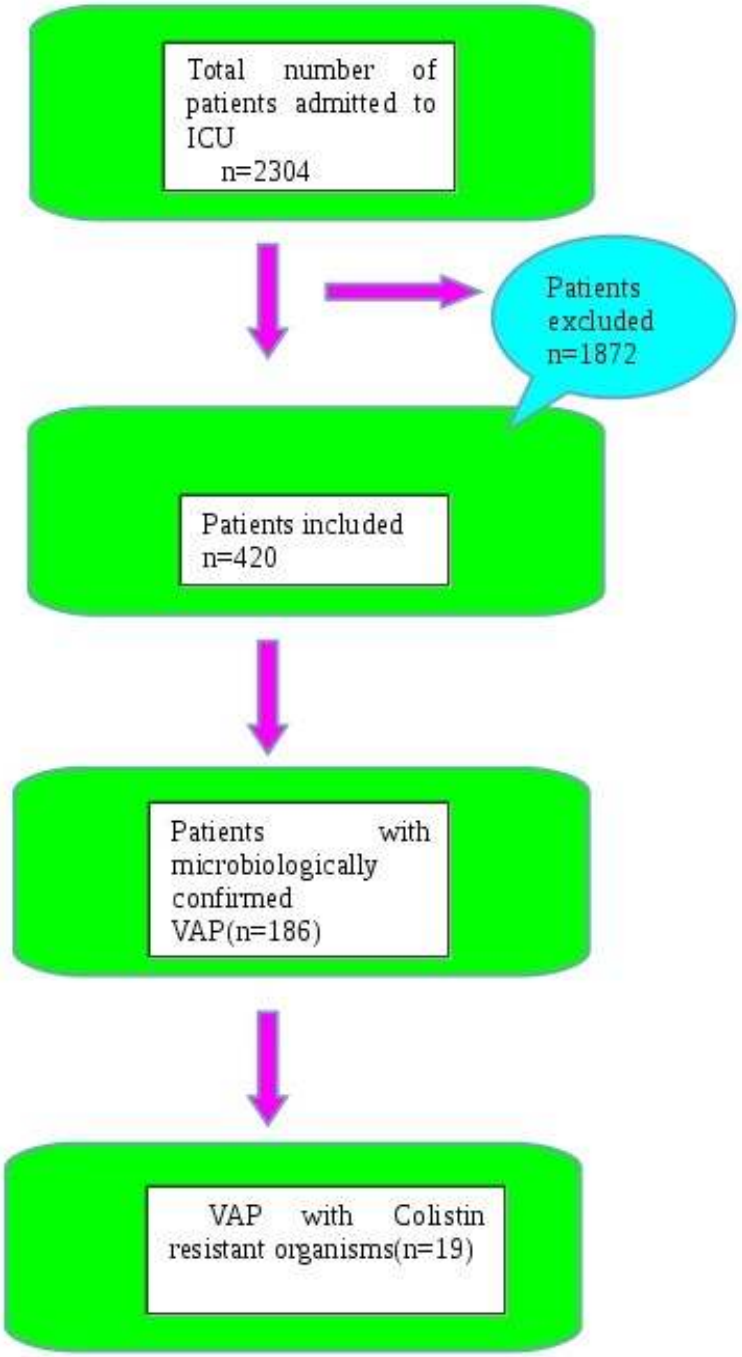
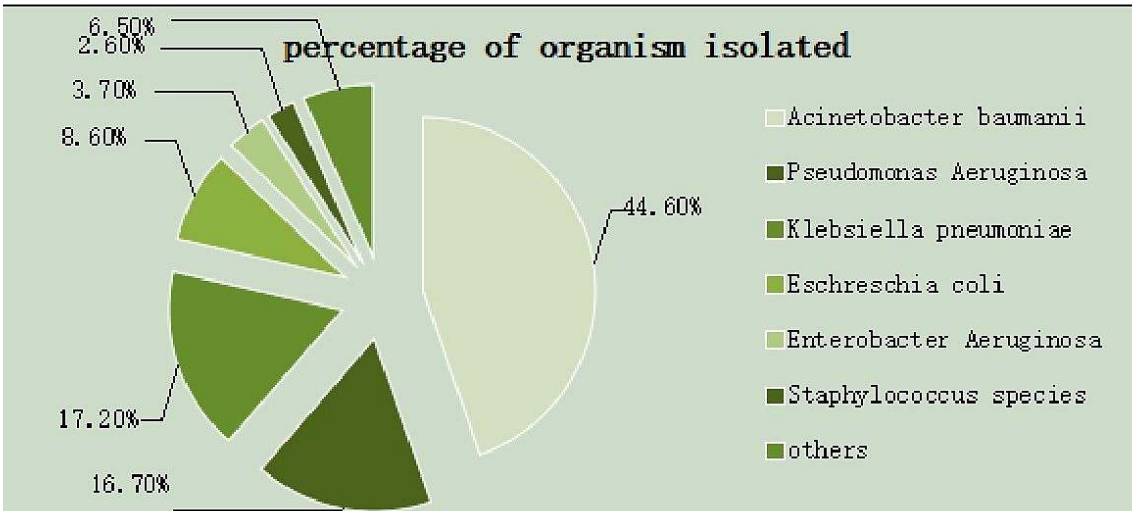


Figure 2. Organisms isolated in patients with ventilator-associated pneumonia



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