

Multi-drug resistant ventilator associated pneumonia: risk factors and outcomes

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ABSTRACT

Background: Multi-drug resistant (MDR) ventilator associated pneumonia (VAP) may lead to inappropriate empiric antimicrobial treatment and poor outcomes. The purpose of this study was to investigate MDR pathogens' effect on the VAP patients in order to improve the treatment choice and outcome.

Methods: We retrospectively studied a collection of 132 VAP patients that confirmed the characteristics, risk factors and outcomes of pneumonia. MDR VAP patients were also compared with non-MDR VAP patients.

Results: MDR and non-MDR pathogens were found in 96 (72.7%) and 36 (27.3%) of the patients, respectively. The most common organism was *Klebsiella pneumoniae* and the most fatal MDR pathogen was *Staphylococcus aureus*. The MDR VAP was found to be associated with an increased length of stay in intensive care unit (ICU), increased hospital stay, and longer intubation time. No statistically significant association was found between prior antimicrobial use and MDR-VAP. The mortality rate of MDR VAPs was significantly higher than non-MDR VAPs.

Conclusion: Discharging patients from ICU and hospital and extubation of the patients as early as possible are two important interventions for prevention of MDR-VAP. Regarding prior antimicrobial use, no significant difference was observed between MDR and non-MDR VAPs. Administration of empiric antibiotic therapy seems to have a protective effect, decreasing mortality without evidence of contributing to multi-drug resistance.

KEY WORDS:

MDR, Outcome, Risk factor, VAP

INTRODUCTION

VAP is a major ICU infection, with an incidence that ranges from 6% to 52%. It is a major factor in high morbidity and mortality and increased financial burden in ICU (1, 2). It occurs in ICU patients after 48 hours or more of endotracheal intubation and mechanical ventilation. By invasive or noninvasive techniques the lower respiratory tract sample is collected to achieve VAP etiologies (3).

The overall rate of VAP in developing countries ICU is 13.6 per 1000 ventilator-days; it is more than four times the VAP rate in US ICUs (4). Nosocomial pneumonia has a complicated microbiological epidemiology. Gram negative bacteria and some gram positive species followed by few anaerobic species are known as the most important pathogens responsible for VAP (5, 6).

Widespread antibiotic resistance among bacteria isolated from VAP patients represents a serious concern as it may lead to higher antimicrobial administration and mortality rate and prolonged stay in the ICU (7, 8). MDR organisms are strongly associated with inappropriate empiric antimicrobial therapy, an important factor of mortality in patients with VAP (1).

European center for Disease prevention and control (ECDC) refers to MDR as an organism non-susceptibility to a minimum of one agent in three or more antimicrobial classes. Based on the ATS/IDSA guideline, early and late onset VAP, are respectively defined as VAPs that occur within and after the first 96 hours of hospitalization (9).

The most prominent risk factors for developing a respiratory nosocomial infection caused by MDR organisms in ICU are: mechanical ventilation, immunosuppression, and recent antibiotic therapy, hospitalization longer than five days (10).

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The main risk factors that prompt VAP development are as follows: recent surgery, use of proton pump inhibitors, prolonged intubation and difficulty in weaning from mechanical ventilation, nasogastric tube placement, supine position of patient, recent use of antibiotic, chronic pulmonary diseases, trauma and previous septicemia, and transportation of the patient outside the ICU (11).

The present study retrospectively assesses the risk factors, responsible organisms and outcomes of MDR VAP in an adult ICU in Iran. Antimicrobial resistance patterns have also been evaluated for the VAP patients.

METHODS

We conducted a retrospective, cross sectional single center study in multidisciplinary ICU of a general hospital in Tehran-Iran. In this hospital antibiotic susceptibility testing by disc diffusion was in accordance with clinical and laboratory standard institute.

First, the lab documentation has been extracted for all tracheal samples sent for VAP between 2010- 2014. The patients, who were intubated for more than 48 hours and had the VAP criteria, were considered as VAP ($T \geq 38$ or $T \leq 36$, profuse or purulent tracheal secretion, new or progressive chest infiltration).

Positive tracheal culture in patients with VAP clinical presentation was a major criteria for being included in this study. We excluded patients without a positive microbial diagnosis and those with fungal or poly microbial tracheal culture (Figure 1).

VAP is a variety of pneumonia that emerges more than 48 hours after endotracheal intubation. The clinical diagnosis of VAP is based on the recognition of two out of the four signs of infection (i.e., fever ≥ 38.5 C, leukocytosis, purulent sputum, crepitation in lungs or impaired gas exchange) developed in patients on mechanical ventilation. When occurred in the first 4 days of intubation, it was called early onset pneumonia (1).

The data extracted from patients' medical records included: demographic data, admission date, and prior antibiotic exposure (all antibiotic agents seven days before VAP infection). Antibiotic sensitivity was reviewed. Microorganisms were considered MDR if they were resistant to more than three classes of antibiotics (cephalosporins, carbapenems, beta lactam- and beta lactamase inhibitors, aminoglycosides, and fluoroquinolones) (1).

Statistical analysis was performed using IBM-SPSS version 16. Continuous variables were expressed as numbers and percentages with mean \pm standard deviation. Independent t-Test was used for comparison of continuous variables and chi-square test was used to compare categorical variables. The difference between groups was considered significant if the p-values were < 0.05 .

RESULT

A total of 330 tracheal aspiration (smear and culture) results were extracted, of which only 191 cases had complete documentation. Of these, 132 patients were confirmed as presenting with VAP criteria (Figure 1). One hundred and thirty two patients who were diagnosed as VAP with positive tracheal aspiration culture have been included in our study.

FIGURE 1: Flow diagram of study inclusion and exclusion of patients

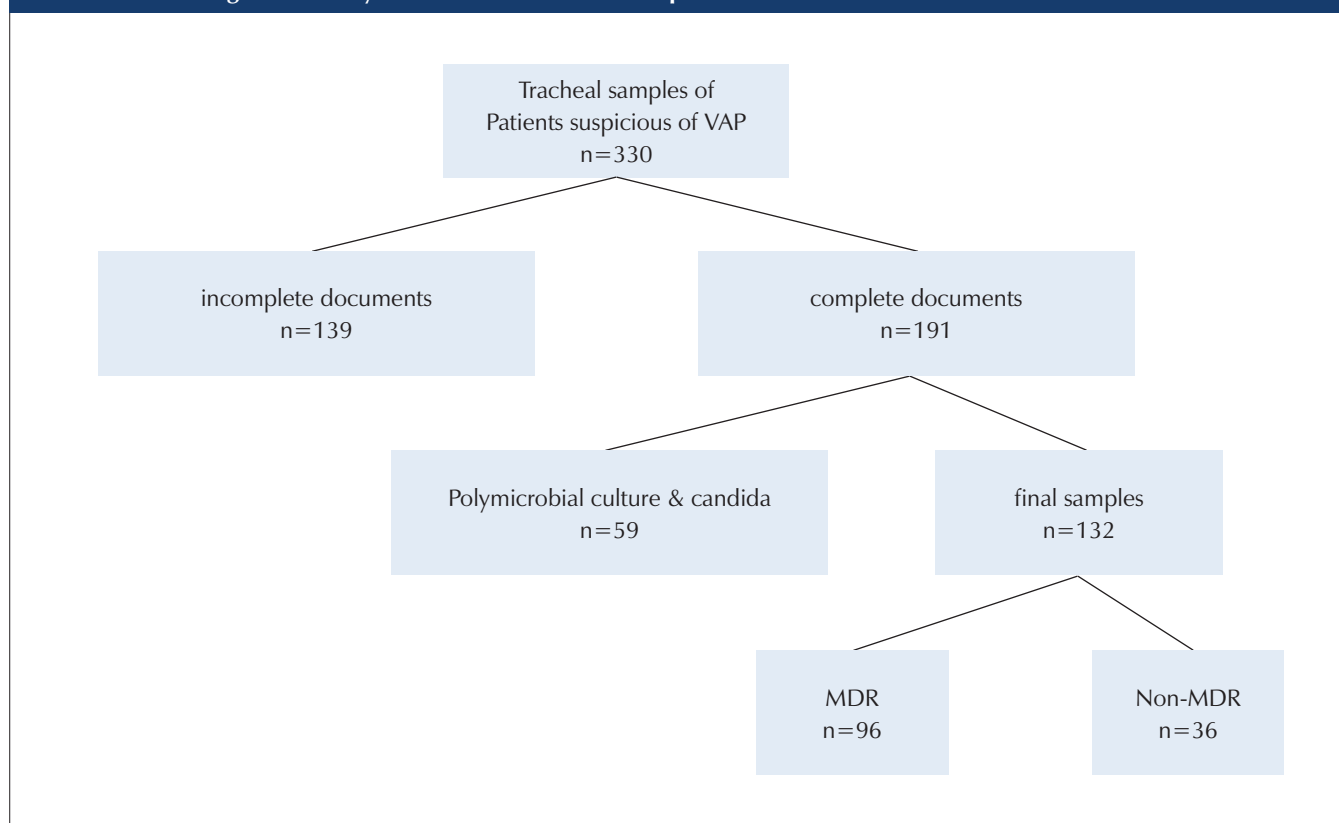


TABLE 1: Baseline characteristic of the MDR and non-MDR VAP patients

		MDR	non-MDR	P-value
Number	132	96(72.7%)	36(27.3%)	
Age, year	54.78± 22.37	57.37±22.66	47.88±20.31	0.030
Male, n	87(65.9%)	64(66.7%)	23(63.9%)	0.762
Female, n	45(34.01%)	32(33.3%)	13(36.1%)	0.762
Intubation time, day	23.94±20.49	28.52±22.68	11.75±8.09	< 0.0001
ICU admission time, day	27.28±23.97	32.11±25.77	14.38±10.62	< 0.0001
Hospital admission time, day	30.42±22.39	35.35±23.64	17.28±10.75	< 0.0001
Antibiotic use before +	94(71.2%)	70(72.9%)	24(66.7%)	0.480
Antibiotic use before -	38(28.8%)	26(27.1%)	12(33.3%)	0.480

The most common organism was *Klebsiella* (26.5%); other prevalent organisms were *Acinetobacter* and *Pseudomonas aeruginosa* (15.2%). 100% of *Acinetobacter spp.*, 85% of *P. aeruginosa*, 75% of *Klebsiella pneumoniae* were MDR organism (Table 2).

Patient characteristics

From 132 samples, 96 cases (72.7%) were MDR and 36 cases (27.3%) were non-MDR. Mean age of the patients was 54.76±22.37 years. The mean age in MDR group was significantly higher than non-MDR ($p<0.05$). Characteristics of patients who developed VAP are shown in Table 1.

Majority of patients were male (65.9%). Patients with MDR were significantly older than non-MDR group. There was no difference between male and female in MDR and non-MDR groups ($p>0.05$; Table 1).

Antibiotic use

There was no significant difference between MDR and non-MDR VAP in viewpoint of previous Antibiotic administration ($P>0.05$; Table 1).

Hospital, ICU stay and Intubation time

The total intubation, ICU and hospital stay time were 23.94±20.49 days 27.28± 23.97 days 30.42±39 days and respectively (Table 1).

Mean time of hospital stay, ICU stay and intubation time in MDR VAP were significantly higher than non-MDR VAP ($p<0.0001$; Table 1).

Blood culture and sepsis

Positive blood culture in the MDR VAP patients (55.2%) have been significantly different from non-MDR VAP patients (19.4%) ($p<0.0001$) however, the rate of sepsis and septic shock have not been very different in these two groups.

Comorbidities

The most common comorbidity was cardiovascular diseases in both MDR and Non-MDR groups. There was no significant difference between the number of comorbidities in MDR and non-MDR VAP ($P=0.204$).

Early and Late onset VAP

Early VAP and late VAP were found to be correlated with non-MDR and MDR patients, respectively (0.012).

Outcome

Mortality rate in the MDR VAP patient (57.3%) has been significantly more than non-MDR group (33.3%) ($p= 0.014$).

The mortality rate between early (30%) and late (70%) onset VAP has not been significantly different ($p= 0.161$).

Acinetobacter pathogens which only were in the MDR group, showed a death rate of 45 % (i.e., 9 cases). *S. aureus* was responsible for the highest death rate (i.e., 63%; 7 cases); however 54% of this pathogen was MDR.

DISCUSSION

VAP MDR pathogens are associated with significant mortality, morbidity and rise of hospital care costs (12). The variables that the present study identified as significant risk factors for acquiring MDR VAP are: the age, intubation time, ICU and hospital admission time.

Out of the 132 tracheal samples (VAP patients), 96 cases (72.7%) were MDR and 36 cases (27.3%) were non-MDR. This high rate of MDR pathogen was similar to other studies (i.e., 51.8%-78.7%) (13,14). Notably, most of our cases were older than the other studies. Patients in the MDR group were significantly older than the non-MDR, as the previous studies indicated (14). The MDR patients' age was rarely found to be less than the non-MDR patients (15).

Some studies suggested that the prior antibiotic use is related to the occurrence of MDR VAP (3, 17-19). However in viewpoint of the previous antibiotic administration, the difference between MDR and non-MDR groups was not significant enough as implied by the former studies (16, 17). The present study only recorded Antibiotic use in the seven days before admission, therefore we cannot exclude the possibility that the earlier use or perhaps prolonged use of Antibiotic might have affected the microbiology of VAP (16).

TABLE 2: Etiologic diagnosis of pneumonia in 132 VAP patients pathogens

Pathogen N(%)	All	MDR	Non-MDR
<i>Acinetobacter</i>	20(15.2%)	20(20.8%)	
Non-Fermenting Gram negative bacilli	7(5.3%)	6(6.2%)	1(2.8%)
<i>Citrobacter</i>	4(3%)	2(2.1%)	2(5.6%)
<i>Staph-coagulase negative</i>	17(12.9%)	4(4.2%)	13(36.1%)
<i>E. coli</i>	3(2.3%)	2(2.1%)	1(2.8%)
<i>Enterobacter</i>	9(6.8%)	8(8.3%)	1(2.8%)
Gram positive cocci	5(3.8%)	2(2.1%)	3(8.3%)
<i>Klebsiella</i>	35(26.5%)	28(29.2%)	7(19.4%)
<i>Proteus</i>	1(0.8%)	1(1%)	
<i>Pseudomonas</i>	20(15.2%)	17(17.7%)	3(8.3%)
<i>Staphylococcus</i>	11(8.3%)	6(6.2%)	5(13.9%)
<i>aureus</i>		96(100%)	36(100%)

Patients who are in the hospital or ICU for a protracted period of time are increasingly exposed to nosocomial pathogens, therefore they are at higher risk for colonization with the organisms (i.e., the isolation of MDR pathogens). At the same time, earlier Antibiotic use that was not regarded in our study protocol, may have contributed to the increased risk of isolation of MDR organisms (15, 16).

Similar to the study carried out in 2016 (20) the most common organism in our VAP patients was Gram negative organisms (Table 2). However, in the USA and Canada the responsible pathogen for VAP was Gram positive (14, 26). The current study found out 85% of *P.aeruginosa* organisms to have been MDR, whereas the former studies indicated lower percentages (14, 21). In the present research, 100% of *Acinetobacter spp.* pathogens were MDR, similar to the study by Dey and Bairy (17). However, in other studies, these were significantly lower, ranging between 40%-52% (12, 14, 18).

The highest mortality rate in the present study belonged to *S. aureus* (55% MDR) with 63.4% incidences. At the same time, the death rate caused by *Acinetobacter spp.* (100% MDR) was 45%. An earlier study indicated an association between the MDR status of pathogens and their mortality rate (27). However, the mortality of VAP caused by *Acinetobacter* does not look to be modulated by its MDR status (28-30).

As regard with the positive blood culture, mortality rate and late VAP, the current study found significant differences between the MDR and non-MDR groups. The MDR pathogens identified in our patients were mostly associated with the late VAP; similar finding is reported by Kuar et al (14).

This study identified no considerable difference between the mortality rate of early and late VAP, it is in contrast with previous study (14). However, in some studies *Acinetobacter* was the most common pathogen in both early and late onset VAP (17).

LIMITATION OF STUDY

1. The present study was a "single center retrospective" research. To achieve a full understanding of the role of pathogen class and MDR in VAP a multicenter prospective study is needed.
2. The present study was based on the identifying the varieties of responsible organism. More precise quantitative cultures of tracheal secretion provide higher confidence in the organisms recovered.
3. The present study utilized a small sample size. A larger sample size yields more reliable statistical numbers for each pathogen.

CONCLUSION

In regard with the prior antimicrobial use, no significant difference is observed between MDR and non-MDR VAP. Therefore administration of empirical antibiotic seems wise, to decrease the mortality, without fearing for occurrence of MDR pathogens. Also no correlation was established between the MDR status of certain pathogen and mortality of the VAP patients. Most of late VAP are linked with MDR organisms, hence, there is no significant difference between early and late VAP in viewpoint of mortality.

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