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An Investigation into the Pattern of Antibiotic Resistance of Bacteria Causing Ventilator – Associated Pneumonia in ICU

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Authors' contributions

This work was carried out in collaboration between all authors. Author BA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TH and OA managed the analyses of the study. Author NE managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: The present study sought to determine the pattern of antibiotic resistance of pathogens in Ventilator–Associated Pneumonia (VAP) and to investigate risk factors of multi-drug resistant (MDR) in ICUs of tertiary referral hospitals.
Study Design: Cross sectional study.
Place and Duration of Study: In this cross sectional study, the files of 196 patients with VAP hospitalized in ICU of tertiary referral hospitals in 2014 were examined.
Methodology: In order to determine common pathogens and their pattern of antibiotic resistance, the patients' results of culturing Bronchoalveolar fluid were examined. The agent pathogens were divided in two groups of with and without MDR and different demographic and risk factors for resistance were compared into the two groups.

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Results: Among from 196 patients examined, 53 and 143 cases had early and late pneumonia, respectively. There was no significant difference between the early and late groups in regard to the frequency of MDR pathogens. There was no significant difference between the two groups with and without MDR in terms of age, gender, immune deficiency, duration of hospitalization and taking antibiotics. The most common early and late types were *Acinetobacter baumannii* (40.4%) and *Klebsiella pneumoniae* (31.8%), respectively and the minimal resistance of the bacteria was related to Colistin and amikacin antibiotics.
Conclusion: Considering the high and increasing prevalence of antibiotic resistance, measures such as providing samples for culture before prescribing antibiotics, starting empirical treatment based on the frequency of agent pathogens and the rate of their antibiotic resistance and avoiding prescription without indication of antibiotics seem necessary.

Keywords: VAP; antibiotic resistance.

ABBREVIATIONS

VAP : Ventilator Associated Pneumonia.
ICU : Intensive Care Unit.
MDR : Multi Drug Resistant.

1. INTRODUCTION

Ventilator Associated Pneumonia (VAP) is the most common nosocomial infection in Intensive Care Unit (ICU) and is created at least 48 hours after the initiation of mechanical ventilation [1].

In general, clinical VAP demonstrations are similar to all other forms of pneumonia: fever, leukocytosis, increasing respiratory secretions and lung density on physical examination along with appearance or change of pulmonary infiltrates on chest x-ray. Other clinical demonstrations may include tachypnea, tachycardia, decreasing oxygenated and increasing minute ventilation [2].

VAP is classified into early and late types. Early form is created less than 4 days after the initiation of mechanical ventilation, while the late one is observed after 4 days [3]. Prognosis and response to treatment is better in the early type than the late one; however, the prevalence of the late type and mortality are more common and the rate of drug-resistance is higher in this type of pneumonia [4].

Today, many cases of nosocomial pneumonia do not respond to conventional antibiotics which causes higher rate of complications and morbidity in these patients. Therefore, identifying the organism of pneumonia and determining the type of effective antibiotics can play a capital role in the prevention of complications and mortality in hospitalized patients [5-7].

The most important microorganisms which lead to pneumonia are *Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Proteus mirabilis, Enterococcus* spp, *Escherichia coli, Enterobacter aerogenes, Citrobacter freundii, Serratia marcescens, Streptococcus viridans* and *Streptococcus* group D*.* Microorganisms causing VAP can include multi-drug resistant (MDR) bacteria. The relative frequency of each bacterium may be significantly different among hospitals, and even vary among various units of ICU in a hospital [2]. Also, risk factors for MDR in VAP include: Length of hospitalization more than 5 days, receiving antibiotics within 90 days before suffering from pneumonia, the high prevalence of antibiotic resistance in ICU and immunodeficiency [8].

Since ICUs in a tertiary referral hospital is host of considerable various patients, it is very important to pay attention to up to date determination of pathogens' antibiotic resistance pattern in VAP, antimicrobial susceptibility of bacteria on ventilator associated pneumonia, epidemiological relevant risk factors, management, budgeting and decision-making. Accordingly, the present study was designed and implemented to determine the pattern of antibiotic resistance as well as MDR risk factors in patients with VAP hospitalized in intensive care units.

2. MATERIALS AND METHODS

The current descriptive cross-sectional study was conducted in in Isfahan Al Zahra Hospital from May 2014 to May 2015. The population included the patients with VAP admitted to the Intensive Care Unit (ICU) in Al Zahra Hospital in Isfahan. Considering the small size of sample population, Census method was used for sampling. Clinical Pulmonary Infection, CPIS Score (fever higher than 38.5, Leukocytosis <11000 or Leukopenia <4000 PaO2/flo2≤ 240), lung radiography (infiltration, density and cavitation), increased

respiratory discharge and cultivation of aspirated Phlegm through tracheal tube) were used to ensure the certainty of VAP diagnosis. According to these scales, a score equal to or above 6 was considered for VAP diagnosis. Therefore, the test results of all the patients hospitalized in ICU, were examined first. 196 patients whose exact date of ventilation, who had a positive bronchoalveolar cultures, and had no signs of pneumonia before connecting to the ventilator were selected. The patients were 119 males and 77 females with the mean age of 57.69±13.06.

After receiving permission from the Research Council and Ethics Committee of Isfahan University of Medical Sciences, the patients' records were studied and the required information including age, sex, date of admission, date of ventilation, pneumonia history, medical history and medication use were extracted. Hospital Information System (HIS) was used to examine the culture results of the patients and antibiogram of bronchoalveolar fluids.

To evaluate some demographic and risk factors of antibiotic resistance in VAP, pathogens were divided in two groups of with and without multidrug-resistance and factors such as age, sex, immunodeficiency and length of hospitalization before suffering from pneumonia were compared among the patients in both groups. Patients were divided into two healthy and immunodeficiency groups using data from history of patient and drug use listed in the patients' records. Patients with the history of diabetes, cancer, chemotherapy, rheumatic disease, organ transplantation and kidney failure were in the immunodeficiency group and others in the healthy one.

2.1 Statistical Analysis

The collected data were analyzed by SPSS Software (Version 20, SPSS Inc; Chicago, IL) using independent t-test, chi-square and the level of significance was considered less than 0.05.

3. RESULTS

Of 196 patients with VAP, 119 (60.7%) cases were males and 77 (39.3%) ones were females with an average age of 57.69±13.06 years (Range: 10-96 years old). The type of pneumonia was early in 53 (27.1%) cases and was late in 143 (72.9%) ones. The results from culturing bronchoalveolar fluids included 314 pathogens. Also, 156 (79.6%) patients had multidrug-resistance and 40 (20.4%) had no MDR, and the most common type of pathogen was *Acinetobacter baumannii* with 64.8% (Table 1).

Table 1. Distribution of demographic characteristics frequency and the results from culturing bronchoalveolar fluids in the studied patients

Variables		Frequency	Percentage
Gender	Male	119	60.7%
	Female	77	39.3%
Age; year (Mean ±SD)		57.69±13.06	
Type of pneumonia	Early Onset	53	27.1%
	Late Onset	143	72.9%
Multi drug resistant	Yes	156	79.6%
	No	40	20.4%
Pathogens	*Klebsiella pneumoniae*	100/196	51%
	Acinetobacter baumannii	127/196	64.8%
	Pseudomonas aeruginosa	24/196	12.2%
	Staphylococcus aureus	25/196	12.8%
	Staphylococcus epidermidis	3/196	1.5%
	Proteus mirabilis	4/196	2%
	Enterococcus spp	9/196	4.6%
	Escherichia coli	10/196	5.1%
	Enterobacter aerogenes	4/196	2%
	Citrobacter freundii	1/196	0.5%
	Serratia marcescens	1/196	0.5%
	Streptococcus viridans	5/196	2.6%
	Streptococcus group D	1/196	0.5%

On the other hand, among from 53 early pneumonias, 42 (79.2%) cases were diagnosed with MDR and 11 (20.8%) ones were without MDR and out of 143 pneumonias, 114 (79.7%) cases were also with MDR and 29 (20.3%) without MDR so that there was no significant difference between the distribution of pathogens frequency with MDR in early and late groups (P-value = 0.942). An investigation into the distribution of frequency of MDR pathogens in both groups showed that in both types of pneumonia, both *klebsiella pneumoniae* and *Acinetobacter baumannii* pathogens had the highest drug resistance than the other pathogens ($P < 0.05$) (Table 2).

In Fig. 1, the percentage of MDR frequency is given by the type of pathogen. Overall, 79.9% of pathogens from culture had multi-drug resistance and among them, *Staphylococcus epidermidis*, *Citrobacter* spp and *Streptococcus* group D had the most MDR (100%).

Table 2. Frequency distribution of pathogens from culturing bronchoalveolar fluids in the patients divided by the type of pneumonia and multi drug resistant

Pathogens	Early onset (n=53)		Last onset (n=143)	
	MDR*(n=42)	Non-MDR* (n=11)	MDR* (n=114)	Non-MDR*(n=29)
Klebsiella pneumoniae	16/42(38.1%)	7/11(63.6%)	56/114(49.1%)	21/29(72.4%)
Acinetobacter baumannii	37/42(88.1%)	1/11(9.1%)	88/114(77.2%)	1/29(3.4%)
Pseudomonas aeruginosa	2/42(4.8%)	3/11(27.3%)	12/114(10.5%)	7/29(24.1%)
Staphylococcus aureus	4/42(9.5%)	1/11(9.1%)	18/114(15.8%)	2/29(6.9%)
Staphylococcus epidermidis	1/42(2.4%)	0/11(0%)	2/114(1.7%)	0/29(0%)
Proteus mirabilis	0/42(0%)	0/11(0%)	0/114(0%)	4/29(13.8%)
Enterococcus spp	3/42(7.1%)	0/11(0%)	3/114(2.6%)	3/29(10.3%)
Escherichia coli	1/42(2.4%)	2/11(18.2%)	2/114(1.7%)	5/29(17.2%)
Enterobacter aerogenes	1/42(2.4%)	2/11(18.2%)	0/114(0%)	1/29(3.4%)
Citrobacter freundii	0/42(0%)	0/11(0%)	1/114(0.9%)	0/29(0%)
Serratia marcescens	0/42(0%)	0/11(0%)	0/114(0%)	1/29(3.4%)
Streptococcus viridans	2/42(4.8%)	2/11(18.2%)	1/114(0.9%)	0/29(0%)
Streptococcus group D	0/42(0%)	0/11(0%)	1/114(0.9%)	0/29(0%)
P	0.002		<0.001	

**: MDR: Multi Drug Resistant, Data shown n/N (%)*

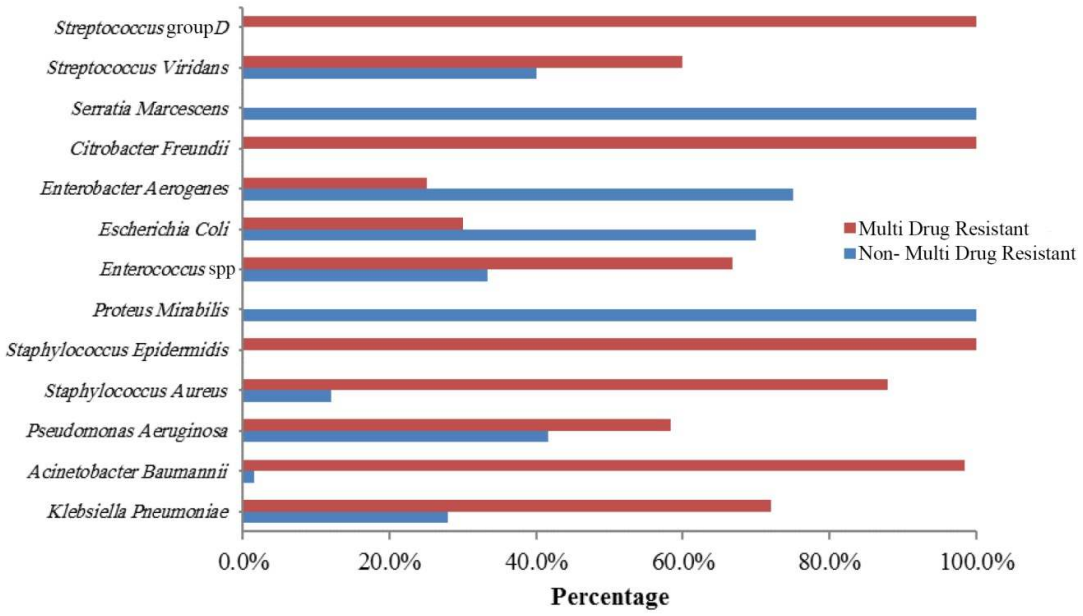

Fig. 1. Bar diagram of the frequency percentage of multi drug resistant in terms of the type of pathogen

Furthermore, the results from logistic regression on the investigation of factors affecting MDR in VAP showed that none of the factors including gender, age, duration of hospitalization and history of disease had a significant role in their antibiotic resistance ($P > .05$). In other words, there was no significant difference in the comparison of two groups with and without multi-drug resistance in terms of the mean age of the patients ($P = .428$), gender ($P = .233$), mean duration of hospitalization before suffering from pneumonia ($P = .546$) and the prevalence of immunodeficiency ($P = .688$) (Table 3).

It should be noted that all patients had the history of antibiotic usage within 90 days before suffering from pneumonia and in this respect; there was no difference between the groups with and without multi-drug resistance.

Finally, the percentage of antibiotic frequency resistance among the most common cases with gram-negative bacteria isolated the culture of bronchoalveolar of patients to the conventional antibiotics in treating patients indicated that the most effective antibiotics are Colistin and Amikacin against common gram-negative bacteria while the highest percentage of resistance has been related to Cefotaxime and Cefepime (Fig. 2). Out of gram-negative bacteria, the most frequency was related to staphylococcus with antibiotic resistances of (0%), (50%), (75%), (85%), (8.7%), (76.2%) and (75%) to Vancomycin, Amikacin, Ciprofloxacin, Oxacillin, Cotrimoxazole, Erythromycin and Tetracycline, respectively.

Table 3. Analysis to investigate the factors influencing antibiotic resistance in ventilator–Associated pneumonia

Factors	Multi drug resistant (n=156)	Non- Multi drug resistant (n=40)	P value
Age; year	57.12±14.22	59.07±12.34	0.428
Gender			
Male	98/156(62.8%)	21/40(52.5%)	0.233
Female	58/156(37.2%)	19/40(47.5%)	
Hospitalization; day	12.81±4.01	13.23±3.56	0.546
History of disease			
Immunocompetent	108/156(69.2%)	29/40(72.5%)	0.688
Immunocompromised	48/156(30.8%)	11/40(27.5%)	

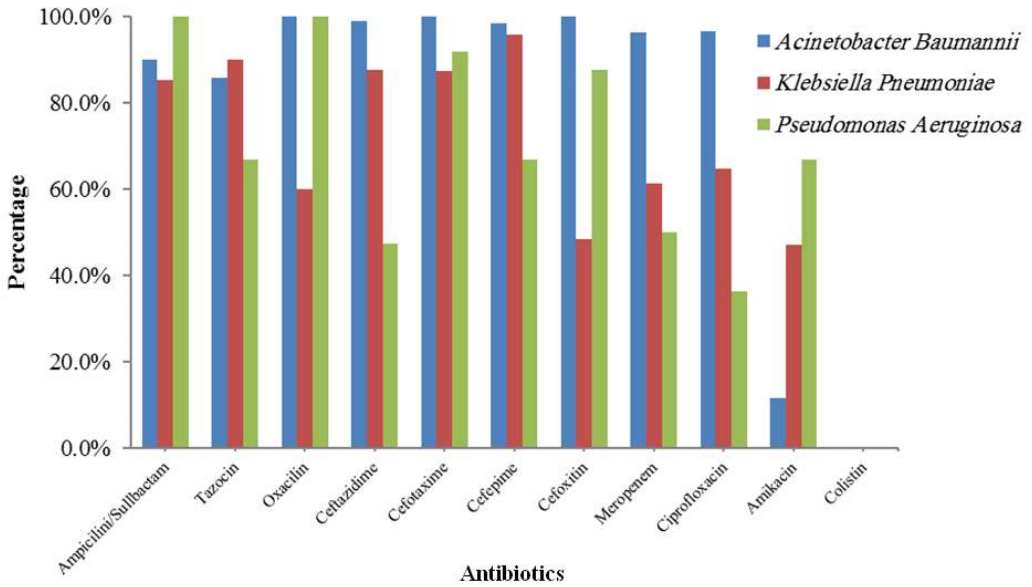

Fig. 2. Bar chart of the frequency percentage of gram-negative bacterial resistant to most common antibiotics

4. DISCUSSION

Today, ventilator-associated pneumonia becomes as one of the most concerns of clinicians. While this complication thought to be decrease due to improvement of diagnosis and treatment approaches, many patients are infected during use of mechanical ventilator which leads to high level of mortality [9]. With the increase of this complication, many investigations were performed in order to defined the main causes of disorder initiation [1,2]. Along with them, we evaluated the presence of pathogen microorganism which was responsible for pneumonia in ICU patients using ventilator. Our findings showed no significant difference between prevalent pathogens and the rate of antibiotic resistance in early and late types while another study stated that antibiotic resistance in late pneumonia was more than the early type [10]. Nseir et al. [11] in 3164 ICU patients found that the number of antibiotic used by late-onset ICU patients were significantly higher than those with early-onset infection. Giantsou et al. [12] Also found in early-onset VAP the number of multiresistant bacteria was noticeably higher than in late-onset VAP. However, Grusan et al. [13] stated that potentially antibiotic resistant gram negative bacteria in early-period were considerably higher than in late-period. Furthermore, in both types of pneumonia, *Acinetobacter baumannii* and *Klebsiella* pneumoniae were the most frequent ones. Likewise [14], most recent study which reported the clinical predictors of VAP in ICU of six Italian hospital found that *Klebsiella* spp. and *Acinetobacter baumannii* were the most frequent pathogens in ICU patients with 19.6% and 18.3% incidence, respectively. However, it has been previously indicated that there was a significant difference in the prevalence of pathogens in the early and late types [10]. Interestingly, in a review which reported 24 studies for a total of 1689 episodes and 2490 pathogens it has been reported that *Pseudomonas aeruginosa* had a highest frequency in VAP (24.4% of total incidence) [15].

Our findings demonstrated that there was no significant difference between the two groups of with and without MDR in terms of the type of pneumonia and in fact in terms of the interval between connection to ventilation and the incidence of pneumonia. Nevertheless, another study reported that the time interval of the pneumonia incidence was connected to the ventilator were different in three groups of sensitive, MDR and XDR. In the sensitive group, it was reported as four days and in the two other groups, it was reported more than 4 days [16].

Our assessment about the influenced factors having direct impact on microbial resistance in VAP revealed that none of gender, days of hospitalization, history of immunocompetent or immunocompromised diseases had effective effect on MDR. Opposed with us, Girish and Michael did a case study on VAP and introduced factors such as the use of antibiotics within 90 days before suffering from pneumonia, immunodeficiency and incidence of pneumonia after 5 days of hospitalization as risk factors for antibiotic resistance in this type of pneumonia [8]. In addition, incidence and outcome in VAP in another study mentioned that those factors are involved in mortality and morbidity of ICU patients [17]. Many studies have stated that reducing on antibiotics administration could be a positive approach for reducing MDR infection and it should be noted that restriction use of unnecessary antibiotics plays a central role in antimicrobial resistance which impose communities the excessive cost [13,18].

Also, the results from the frequency percentage of the most common gram-negative bacteria's resistance obtained from bronchoalveolar patients compared to common antibiotics in the treatment showed that the most effective antibiotics against these bacteria are Colistin and Amikacin. In gram-positive bacteria, the most common type in this study was *Staphylococcus aureus* that showed the least resistance to Vancomycin (0%) and Cotrimoxazole (8.7%). In this regard, the results of the study by Afkhamzade et al were not much different with those of this study in terms of resistance of *Klebsiella pneumoniae* to Cephalosporins, Ciprofloxacin and Amikacin [19] while on *Acinetobacter baumannii*, the resistance score to Ciprofloxacin and Ceftazidime was more in our study. Moreover, the resistance of *Pseudomonas aeruginosa* to the two Cefotaxime and Amikacin antibiotics was higher in our study. The comparison of another study [20] with our findings also indicated an increase in the resistance of *Klebsiella pneumoniae* to Ciprofloxacin and Amikacin antibiotics. Also, the resistance of Staphylococcus aureus to vancomycin has been previously reported 14.3% [20], while in our study there was no *Staphylococcus aureus* resistant to Vancomycin. What's more, the resistance of the bacteria to

Ciprofloxacin and Erythromycin was reported significantly higher than other antibiotics, however, as mentioned before, Vancomycin and Cotrimoxazole earned the lowest beneficial antibiotics on VAP [20].

Finally type of pathogens screened in our study seemed good; however we thought that our limitation would be a relatively small investigated population. We think that using of more centers in various places would be a good suggestion for further studies. Furthermore, due to various reports regarding to different incidences of pathogens among studies the role of other factor such as environmental elements as well as knowledge of intensive care unit nurses about how to decrease the incidence of infection by performing international health protocols and also evaluation of knowledge of doctors about multi-drug resistant bacteria should be integrated in next investigations.

5. CONCLUSION

Patients in ICUs have weaker body than others in other hospital sections. It causes opportunistic pathogens can infect them easier. Pneumonia is the most common outcome of these invasive pathogens. They need more effective antimicrobial agents such as antibiotics. Given the results of this study and comparing them with other studies in this area, and regarding to the high incidence and increasing antibiotic resistance, the measures such as providing samples for culture before prescribing antibiotics, starting empirical treatment based on the frequency of agent pathogens and the rate of their antibiotic resistance and avoiding prescription without indication of antibiotics seem necessary.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Isfahan University of Medical Sciences' Ethical Committee with the code of 394749.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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