

Original Article

Ventilator-associated Pneumonia: Multidrug Resistant *Acinetobacter* vs. Extended Spectrum Beta Lactamase-producing *Klebsiella*

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) has been considered as a healthcare-associated infection with high mortality. *Acinetobacter baumannii* and *Klebsiella pneumoniae* are the common causes of VAPs around the world.

Methodology: This research was a retrospective observational study in the intensive care unit (ICU) in a tertiary referral collegiate hospital in Tehran between March 2016 and May 2018. Patients who fulfilled VAP due to documented Multidrug Resistant *Acinetobacter baumannii* (MDR-AB) or Extended Spectrum Beta Lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) criteria were enrolled. General demographic features, duration of hospital stay, antimicrobial treatment regimens, duration of ICU admission, the period of mechanical ventilation (MV) and 30-day mortality were documented and compared.

Results: 210 patients were found with clinical, microbiological and radiological evidence of VAP. In total, 76 patients with MDR-AB and 76 patients with ESBL-KP infections were matched in the final analysis. Duration of hospitalization in the patients with MDR-AB was significantly more than that of patients infected with ESBL-KP (p -value: 0.045). Patients diagnosed with MDR-AB VAP had a 65.8% mortality rate compared to 42.1% in the ESBL-KP infection group ($p = 0.003$).

Conclusions: Results of the present study demonstrated that VAPs caused by MDR-AB may be more hazardous than ESBL-KP VAPs because they could be accompanied by a longer hospitalization course and even a higher mortality.

Key words: Ventilator-associated Pneumonia; drug Resistance; *Acinetobacter baumannii*; *Klebsiella Pneumoniae*.

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Introduction

Pneumonia is one of the major causes of death around the world [1]. In a survey conducted between 2010 and 2014 in the United States, the most common lower respiratory system infection was community-acquired pneumonia (CAP) (54.3%) and ventilator-associated pneumonia (VAP) had the lowest prevalence (1.6%), but the mortality rate related to CAP was 7.9% while for VAP it was about three folds (21.6%) higher [2]. VAP has been considered as a sub-category of the healthcare-associated infections (HAIs), which is defined as a lower respiratory tract infection occurring after at least 48 hours of tracheal intubation [3].

Although *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* remain among common etiologic agents of VAP, *Acinetobacter baumannii* (AB) and *Klebsiella pneumoniae* (KP) are known as the most important causes of VAP in many ICUs all around the world [4-10]. Due to the high ability of these two microorganisms for creating resistance against many antibiotics, they could be associated with high mortality rate [1,11]. In spite of increasing our knowledge about the causes and agents of VAP and even its prevention, this lower respiratory infection is still a serious complication of ICU admitted patients and the need to

study the different aspects of the infection can also be considered [12]. We thought that the clinical course comparison of two mentioned microorganisms may be effective to manage the infected patients in ICU. To our knowledge, no studies have compared patients who develop VAPs regarding these two agents. To meet this gap, we designed a matched case-control study to compare the patients diagnosed with VAP caused by AB and KP based on their microbiologic profile and outcomes. We analysed differences with regards to the duration of hospital and ICU stay as well as the days on mechanical ventilation.

Methodology

Study Design and Setting

This was a retrospective observational study conducted in a tertiary referral collegiate hospital in Tehran, Iran. All clinical data of the patients who were under mechanical ventilation in ICU from March 2016 to May 2018 were systematically analysed and the patients who fulfilled the following criteria were enrolled in the study: 1) age >18 years; 2) Patients admitted in ICU; 3) Their radiologic studies (chest X-rays) showed newly formed consolidation or other signs of parenchymal involvement; 4) VAPs due to documented MDR-AB or ESBL-KP. In this study, Pneumonia was diagnosed based on the following criteria: 1) a new radiographic infiltrate compatible with pneumonia, 2) the presence of symptoms of a lower respiratory tract infection, and 3) the presence of at least one of these items: fever (body temperature > 38°C), leucocytosis (WBC > 11.0x10⁹/L), leukopenia (WBC < 3.5x10⁹/L), purulent sputum or a decreasing in the respiratory compliance and VAP was defined as follows: pneumonia in the patient who did not involve with pneumonia at the onset of intubation and presented features consistent with pneumonia 48 hours after intubation [13]. Clinical samples used to detect causative microorganisms (MDR-AB or ESBL-KP) included blood, sputum, tracheal secretions, broncho-alveolar lavage (BAL) and pleural fluid specimens. In the current study, MDR-AB was defined as the isolate

resistant to at least three classes of antimicrobial agents - all penicillins and cephalosporins, fluoroquinolones, and aminoglycosides [14]. Detection of ESBL producing isolates of KP was based on the results of phenotypic confirmatory test as instructed by Clinical and Laboratory Standard Institute (CLSI) [15]. The general demographic features (age, gender, etc), duration of hospital stay, antimicrobial treatment regimens, duration of ICU admission, the period of time on mechanical ventilation and all-cause 30-day mortality rates were documented for all patients who met the inclusion criteria. The patients suspected for VAP received empirical antibiotics (combination of a carbapenem or piperacillin-tazobactam, an aminoglycoside or fluoroquinolone, and vancomycin). Then, based on the antibiogram of the isolated organisms, antibiotic regimens were selected for patients' treatment.

Data Analysis

All data were entered into the Statistical Package for the Social Sciences software (SPSS version 16.0). Mean and standard deviation (SD) were used to report quantitative variables. We utilized percentage and frequency to show qualitative variables. Independent T-tests and Chi-Square tests were performed to compare groups and odds ratios (with confidence intervals) were measured to achieve study goals.

Ethical Considerations

Data regarding the microbiologic records of patients were gathered by a blinded investigator; code matching to retrieve patient records performed by another researcher who filled checklists anonymously. The study protocol was approved by Institutional Review Boards of Tehran University of Medical Sciences.

Results

During the study period, a total of 210 patients were found with clinical, microbiological and radiological evidence of proven VAP and checked for inclusion and

Table 1. Comparing VAPs caused by MDR-AB vs. ESBL-producing-KP.

	MDR-AB VAP (N = 76)	ESBL-producing-KP VAP (N = 76)	p-value
Age (mean ± SD) (years)	56.6 ± 23.8	55.1 ± 26.5	0.610
Gender (M/F) (%)	52/24 (68/32)	47/29 (62/38)	0.083
Length of Stay (mean ± SD) (days)	41.7 ± 22.5	35.1 ± 19.1	0.045
ICU stay (mean ± SD)(days)	31.9 ± 23.4	26.2 ± 17.3	0.035
Mechanical Ventilation (mean ± SD) (days)	31.1 ± 22.3	28.5 ± 17.1	0.400
Antibiotic Therapy (mean ± SD) (days)	14.2 ± 4.1	11.1 ± 3.6	0.095
Crude Mortality Rate (No. (%))	50 (65.8)	32 (42.1)	0.003

VAP: Ventilator-associated pneumonia; MDR: Multi-drug resistant; AB: Acinetobacter baumannii; ESBL: Extended Spectrum Beta Lactamase; KP: Klebsiella pneumoniae.

exclusion criteria. In total, 76 patients with MDR-AB and 76 controls with ESBL-KP were evaluated in the final analysis. The mean age of the patients was 56, and 35% of them were women and the rest (65%) were men (Table 1). There were no significant differences between two groups regarding age, sex and underlying diseases (p -value > 0.05). Duration of hospitalization in the patients with MDR-AB was significantly more than that of infected with ESBL-KP (Independent T test, p -value: 0.045). Comparison with regards to duration of ICU stay was significantly different between two groups (p -value: 0.035). The average time on mechanical ventilation in the cases with MDR-AB was 31 days which on average is about 3 days more than ESBL-producing KP VAPs. In order to examine the significance of this difference, Independent T test used and the difference was not significant (p -value: 0.4). The main antibiotics used for treatment of MDR-AB VAPs were meropenem (83%), amikacin (79%), ampicillin-sulbactam (58%), and colistin (51%); and main antibiotics used for treatment of ESBL-KP VAPs were meropenem (88%), amikacin (81%), piperacillin-tazobactam (12%), and colistin (8%). Significantly, colistin more likely prescribed for patients with MDR-AB in comparison with ESBL-KP cases (p -value: 0.034). According to antibiotic regimens, there were no significant differences in mortality. The average duration of antibiotic therapy was different between two groups, but this difference was not significant (14 days for MDR-AB VAPs and 11 days for ESBL-producing KP cases). Patients diagnosed with MDR-AB had a 65.8% mortality rate compared to 42.1% in the ESBL-KP group ($p = 0.003$). Mortality odds ratio in MDR-AB VAPs was 2.64 folds more than ESBL-KP cases (95% confidence interval: 1.3-5.1).

Discussion

Determination of the exact incidence of VAP is difficult given that it is often misleading with other respiratory infections like tracheobronchitis [13]. In some studies, near 50% of patients with healthcare-associated pneumonias (HAPs) are VAPs and most likely to occur early in the hospitalization course. As the days on mechanical ventilation raises, the incidence of this hospital acquired infection increases (The average is 5-7 days from the initiation of MV) [16]. In the previous studies, the most common causes of HAPs and VAPs were *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*, but recent studies have shown an increase in the prevalence of *Klebsiella pneumoniae* and *Acinetobacter* species [11,17-19]. Resistance of AB

and KP to Carbapenems is a challenging topic for the clinicians and infectious diseases control teams [11,20].

The main strength of the present study was the matched case-control design. The comparisons made between patients infected by MDR-AB and ESBL-KP as the two most important and common agents of VAPs. To our knowledge, no studies have compared patients who develop VAP with regards to these two responsible agents. Similar studies have been conducted on the comparison of hospital-acquired infections (other than VAP) due to these two MDR microorganisms. For example, in the study by Perez *et al.* that conducted between 2007 and 2008 in Ohio, two groups of patients with carbapenem-resistant *Acinetobacter baumannii* (37 cases) and *Klebsiella pneumoniae* (28 cases) infections were compared with each other [11]. *Acinetobacter baumannii* was isolated in higher rate in the pneumonia patients, while urinary tract was the most common among patients infected with *Klebsiella pneumoniae*. The average length of hospital stays for *Acinetobacter baumannii* and *Klebsiella pneumoniae* were about 24 days and 16 days respectively [11]. However, similar results were obtained in our research (41.7 vs. 35.1). In a study between 2000 and 2003, the average residence days in hospitals following bacteremia of 112 patients with *Acinetobacter bacteremia* (32 days) were compared with 90 patients with bacteremia caused by *Klebsiella pneumoniae* (22 days) and the difference was not significant, while the average of hospitalization days in our patients with MDR-AB VAPs was significantly more than that of the cases infected with ESBL-KP VAPs (42 days vs. 35 days) [21].

In a study comparing *Acinetobacter pneumoniae* with pneumonia due to other agents, when patients had taken appropriate antibiotic therapy, there was no difference in mortality rate between two groups. Also in our patients, between the antibiotic regimens and mortality rate were not significantly different [21]. Antibiotic treatment course for VAP is usually 7 days and it has been shown that this timing schedule has not been associated with higher mortality rate in comparison with longer periods [12]. This fact was also seen in our study: while our patients in both groups received longer days than standard treatment course, longer antibiotic therapy did not affect the patient's outcome.

In another study of Russo *et al.*, clinical manifestations, treatment, and outcome of septic shock patients have been retrospectively compared between two groups of infections with *Acinetobacter baumannii* and *Klebsiella pneumoniae* [22]. 220 patients

participated in this study and mortality rate, such as our study, was significantly different between the two groups and was higher in the cases with *Acinetobacter baumannii* (84.8% vs. 44.5%, $p < 0.001$) [22].

In conclusion, the results of the present study showed that VAPs caused by MDR-AB could be accompanied by a longer hospitalization course and ICU staying days and even a higher mortality rate when compared with ESBL-KP VAPs. All these findings suggest that it is crucial to know more about MDR-AB behaviour and try to prevent its spreading.

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