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Original Article

Incidence and predictors of 14-day mortality in multidrug-resistant *Acinetobacter baumannii* in ventilator-associated pneumonia

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) caused by multidrug-resistant *Acinetobacter baumannii* (MDR-AB) is common in hospitals and impacts patient survival. We determined the incidence of MDR-AB VAP in critical care units and examined the predictors of 14-day mortality in these patients.

Methodology: A retrospective case series study was conducted at a tertiary referral teaching hospital in north Jordan. A list of patients with a positive culture of *A. baumannii* between January 2007 and June 2013 was retrieved using computerized hospital databases. Medical records of all these patients were reviewed, and cases of VAP infected with MDR-AB were identified. Predictors of 14-day mortality were determined using multivariable logistic regression adjusted for possible confounders.

Results: Out of 121 *A. baumannii*-VAP cases, 119 (98.3%) were caused by MDR-AB. The incidence rate of MDR-AB VAP was 1.59 cases per 100 critical care unit admissions. The mortality of *A. baumannii*-VAP cases in critical care units was 42% (50/119). Being prescribed two or more definitive antibiotics (prescribed based on susceptibility data) (OR = 0.075, 95% CI = 0.017–0.340, p = 0.001) and ipratropium/salbutamol during mechanical ventilation (OR = 0.140, 95% CI = 0.028–0.705, p = 0.017) were independently associated with lower hospital mortality.

Conclusions: Our results suggest incidence of MDR-AB VAP in critical care units is high and that prescription of antibiotics based on antibiotic susceptibility and use of bronchodilators is associated with lower mortality in this population. Larger prospective studies are needed to explore whether these findings can be replicated in different clinical settings.

Key words: multidrug-resistant *A. baumannii*; VAP; mortality.

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Introduction

Patients who are admitted to critical care units (CCUs) (intensive care unit [ICU], coronary care unit, cardiac ICU, and general intermediate care unit) are highly predisposed to nosocomial infections [1]. Ventilator-associated pneumonia (VAP) is considered one of the most common infections in these units [2]. The estimated incidence of VAP varies among different countries, ranging from 3% to 47% [3,4], with a mortality of 16% to 70% [3,5,6]. *Acinetobacter baumannii*, a Gram-negative coccobacillus, is increasingly becoming one of the most common pathogens causing VAP [2,5]. It is responsible for about 5% to 10% of VAP cases occurring in the ICU [7] and is associated with high ICU mortality (61%) [5].

Worldwide, multidrug-resistant *A. baumannii* (MDR-AB) isolates are emerging [8,9] (*i.e.*, *A. baumannii* isolates non-susceptible to at least one agent in three or more antimicrobial categories [8]). Published data suggest that mortality associated with MDR-AB infections ranges from 14.3% to 49% [9-11], leading to significantly extended ICU and overall hospital stays as well as high healthcare costs [12-14]. Young *et al*. found that patients infected with MDR-AB had a mean of US $60,913 additional charges and 13 extra days of hospital stay [12]. It has been reported that VAP caused by *A. baumannii* or infection by another MDR pathogen was significantly associated with hospital mortality [2]. Prior studies have examined the predictors of mortality in patients with MDR-AB infections [11,15]. Bacteremia,

inappropriate use of antibiotics, age, co-morbidities, number of intravascular lines, number of days of ventilation, and severity of illness have all been identified as determinants of mortality in MDR-AB patients [11,15]. However, the association between these factors and mortality in patients with MDR VAP has not been determined. The study aimed to investigate the incidence of MDR-AB VAP in CCUs and the predictors of 14-day mortality in these patients. A secondary objective was to assess the patterns of antibiotic susceptibility of *A. baumannii* isolates.

Methodology

Study setting

This retrospective case series study was conducted at King Abdullah University Hospital, a 497-bed tertiary referral teaching hospital in north Jordan with an annual average admission rate of 34,291 patients. The study was approved by the ethics committee in Jordan University of Science and Technology (2/64/2013).

Case selection

Cases were identified using computerized hospital databases. Patients who were ≥ 16 years of age, admitted to a CCU, and diagnosed with VAP caused mainly by *A. baumannii* isolates from bronchial wash, sputum, and pleural fluid between 1 January 2007 and 30 June 2013 were included. Pneumonia was considered VAP if the onset occurred ≥ 48 hours after intubation and was diagnosed based on new or progressive pulmonary infiltrates on chest X-ray and two or more of the following: fever > 38°C or hypothermia < 35.5°C, leukocytosis > 12,000 cells/mL or leukopenia < 4,000 cells/mL, purulent bronchial secretions; and supported by the result of a qualitative culture test (positive for *A. baumannii* isolate) [16].

For patients who developed more than one isolate of *A. baumannii*, only the first isolate was considered. Patients with polymicrobial infections or with VAP caused by another microorganism before *A. baumannii* during the same hospital stay were excluded from the study. MDR-AB was defined as *A. baumannii* isolate non-susceptible to at least one agent in three or more antimicrobial categories [8]. Cases infected with MDR-AB VAP were divided, based on their clinical outcome on day 14 from the onset of VAP symptoms, into two groups. Cases who survived on day 14 were classified as the survival group, and cases who did not survive to day 14 of the onset of VAP were classified as the non-survival group. Ventilator care bundle for prevention of VAP [17,18] was adopted in the hospital institution in 2007; interventions include 1) no ventilatory circuit change unless specifically indicated; 2) strict use of hand hygiene with alcohol; 3) use of appropriate educated and trained staff; 4) daily assessment of sedation medication; 5) oral care with chlorhexidine; 6) appropriate cuff pressure check at least every 24 hours; and 7) head of bed elevation of 30 degrees.

Data collection

The required information for each patient was obtained by reviewing patients' files (initial admission assessment, critical care progress notes, medications sheet, nursing notes, and physicians' orders) and computerized laboratory results. *In vitro* susceptibility of *A. baumannii* isolates was identified by the microbiology laboratory in the hospital. The following demographic and clinical data were collected and evaluated as possible predictors of hospital mortality: gender, age, body mass index, co-morbidities, previous hospitalization (admission to hospital within 90 days prior to the present hospital admission) [19], recent invasive procedure (a procedure performed within the 48 hours preceding the positive culture of MDR-AB) [19], acute physiology and chronic health evaluation II (APACHE II) score at CCU admission day (higher score indicates poorer health functioning), primary CCU admission diagnosis, Glasgow coma scale at VAP day (coma was defined as Glasgow coma scale less than 9) [20], prior antibiotics used (receiving an antibiotic for at least 48 hours during the hospital or CCU stay) [4], length of stay in hospital before VAP, length of stay in CCUs before VAP, duration of mechanical ventilation (MV) before VAP, drug use during MV, and empirical antibiotic use (antibiotic that is given before the causative agent is identified) and definitive antibiotic use (antibiotic that is given when the causative pathogen is known and based on susceptibility data) treatments received after VAP.

Microbiology identification

Identification of *A. baumannii* isolates and antibiotic susceptibility were performed (manually and automatically) in the hospital microbiology laboratories according to the Clinical and Lab Standards Institutes (CLSI) guidelines [21]. The type of isolate was identified manually using IMViC tests (indole test, methyl red test, Voges-Proskauer test, and citrate test), and the Kirby-Bauer disk diffusion method was utilized to determine the sensitivity of the identified isolate to tested antibiotics. Both the

identification and susceptibility testing were done automatically using the VITEK2 compact microscan system.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as numbers and percentages. The incidence rate of MDR-AB VAP was calculated by dividing the total number of MDR-AB VAP cases by the number of CCU admissions and multiplying that number by 100. The predictors of 14-day mortality were examined using the T test or Mann-Whitney (continuous variables) and Chi-square (χ^2) test or Fisher's exact test (categorical variables) as appropriate. In order to determine factors that were independently associated with mortality, logistic regression (LR) analysis was performed using the enter method. All variables with $p \leq 0.05$ on univariate analysis were included in the logistic regression model. Odds ratio (OR) values and their 95% confidence intervals (95% CI) were calculated. All tests were two-sided, and statistical significance was set at $p \leq 0.05$. All analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 20.

Results

During the study period, a total of 208 cases with positive culture of *A. baumannii* were identified. Eighty-seven cases were excluded because they did not meet VAP criteria (66.6%; 58/87), were pre-infected by another pathogen (9.2%; 8/87), had inadequate data availability (9.2%; 8/87), or for other reasons (15%; 13/87), leaving 121 cases that met the study inclusion criteria. Of the 121 cases diagnosed with *A. baumannii*-VAP, 119 (98.3%) were caused by MDR-AB. Most cases were patients admitted to the ICU (78%; 93/119), followed by coronary care unit (10%; 12/119), cardiac ICU (6%; 7/119), and general intermediate care unit (6%; 7/119). In the current study, the overall incidence rate of MDR-AB VAP was 1.59 cases per 100 CCU admissions.

Table 1 outlines detailed demographic and clinical characteristics of all cases enrolled in the study. More than half of included patients (63.9%) had at least one co-morbid disease. All patients received at least two drugs while they were receiving MV; the average number of drugs used was 6.6 ± 2.22 (range 2–13). Empirical therapy was used in all patients (100%), while definitive therapy was administered in 64.7% of patients (77/119). Fluoroquinolones were the most commonly used empirical agents (59.7%; 71/119), and colistin (64.9%; 50/ 77) was the most commonly used definitive antibiotic.

Table 1. Demographic and clinical characteristics of patients.

Variable[a] (n = 119)	Count
Gender	
Male	64 (53.8%)
Female	55 (46.2%)
Age at admission (years)[b]	55.5 ± 21.01 (17–96)
Body mass index[b,c]	28.0 ± 6.79 (16.7–57.2)
Current smoker	23 (19.3%)
Drug allergy	5 (4.2%)
Presence of co-morbidities	76 (63.9%)
Hypertension	55 (46.2%)
Diabetes mellitus	39 (32.8%)
Coronary artery diseases	22 (18.5%)
Number of co-morbidities[b]	1.3 ± 1.26 (0–4)
Drugs used during MV	119 (100%)
Number of drugs used during MV[b]	6.6 ± 2.22 (2–13)
APACHE II score on unit admission[b,d]	18.9 ± 9.12 (0–43)
Recent invasive procedure	114 (95.8%)
Number of recent invasive devices[b]	1.8 ± 0.76 (0–4)
Previous hospitalization	38 (31.9%)
Patients transferred from other hospital	32 (26.9%)
Glasgow coma scale < 9 at VAP day	90 (76.9%)

APACHE: acute physiology and chronic health evaluation; MV: mechanical ventilation; VAP: ventilator-associated pneumonia; [a] All data expressed as n (%) of patients unless otherwise indicated; [b] Data described as mean ± standard deviation (SD); (range);[c] Data described for 98 cases (missing for 21 cases); [d] Data described for 103 cases (missing for 16 cases) .

Table 2. Univariate analysis of 14-day mortality in MDR-AB VAP.

Characteristics[a]	Survival (n = 69)	Non-survival (n = 50)	P value
Male	40 (58%)	24 (48%)	0.282
Age (years)[b]	54.7 ± 22.69	56.7 ± 18.59	0.589
Body mass index[b,c]	26.7 ± 6.68	29.9 ± 6.58	**0.023**
Co-morbidities	43 (56.6%)	33 (43.4%)	0.680
Previous hospitalization	21 (30.4%)	17 (34%)	0.681
Number of recent invasive devices[b]	1.7 ± 0.73	1.8 ± 0.80	0.475
APACHE II score on unit admission[b,d]	17.3 ± 8.01	21.1 ± 10.17	**0.045**
Primary unit admission diagnosis			0.07
Neurosurgical	27 (39.1%)	11 (22%)	
Surgical	8 (11.6%)	12 (24%)	
Medical	34 (49.3%)	27 (54%)	
Glasgow coma scale < 9 at VAP day	51 (76.1%)	39 (78%)	0.057
Prior antibiotic use	61 (88.4%)	43 (86%)	0.696
Hospital length of stay before VAP (days)[b]	8.1 ± 7.92	10.4 ± 9.62	0.194
Unit length of stay before VAP (days)[b]	6.7 ± 5.96	8.2 ± 7.79	0.229
MV duration before VAP (days)[b]	5.4 ± 4.55	5.6 ± 4.74	0.786
Drugs used during MV			
Sedative agent	65 (94.2%)	46 (92%)	0.636
Analgesic	32 (46.4%)	18 (36%)	0.258
H_2-blockers or proton pump inhibitors	66 (95.7%)	50 (100%)	0.135
Vasopressor	30 (43.5%)	32 (64%)	**0.027**
Ipratropium/salbutamol nebulizer	23 (33.3%)	7 (14%)	**0.017**
Aspirin	5 (7.2%)	11 (22%)	**0.020**
Number of drugs used during MV[b]	6.4 ± 2.10	7.2 ± 2.30	**0.032**
Number of empirical antibiotics[b]			0.371
1 antibiotic	12 (17.4%)	6 (12%)	
2 antibiotics	22 (31.9%)	22 (44%)	
≥ 3 antibiotics	35 (50.7%)	22 (44%)	
Number of definitive antibiotics[b]			**< 0.001**
None	14 (20.3%)	26 (52%)	
1 antibiotic	11 (15.9%)	11 (22%)	
≥ 2 antibiotics	44 (73.8%)	13 (26%)	

APACHE: acute physiology and chronic health evaluation; MV: mechanical ventilation; VAP: ventilator-associated pneumonia; [a] All data expressed as n (%) of patients unless otherwise indicated; [b] Data described as mean ± standard deviation (SD); [c] Data described for 98 cases (missing for 21 cases); [d] Data described for 103 cases (missing for 16 cases).

Table 3. Multivariable analysis of factors predicting 14-day mortality.

Factors	OR	95% CI	P value
Body mass index[a]	1.048	0.958–1.146	0.308
APACHE II score on unit admission[b]	1.029	0.956–1.107	0.446
Vasopressor during MV	2.324	0.618–8.743	0.212
Ipratropium/salbutamol nebulizer during MV	0.140	0.028–0.705	**0.017**
Aspirin during MV	3.398	0.534–21.609	0.195
Number of drugs used during MV	1.234	0.919–1.657	0.162
Number of definitive treatments			
None	Ref.		
1 antibiotic	0.393	0.084–1.834	0.235
≥ 2 antibiotics	0.075	0.017–0.340	**0.001**

CI: confidence interval; MV: mechanical ventilation; OR: odds ratio; [a] Data described for 98 cases (missing for 21 cases); [b] Data described for 103 cases (missing for 16 cases).

The 14-day mortality among patients infected with MDR-AB VAP was 42.0% (50/119). The results of the univariate analysis of predictors of mortality are shown in Table 2. There were significant differences between 14-day mortality and body mass index ($p = 0.023$) and APACHE II score at CCU admission ($p = 0.045$), with higher body mass index and APACHE II score in the non-survival group compared to the survival group. More cases in the non-survival group used aspirin and vasopressors and more drugs while on MV ($p = 0.020$, $p = 0.027$, and $p = 0.032$, respectively). In contrast, more cases in the survival group had used an ipratropium/salbutamol nebulizer during MV ($p = 0.017$) compared to the non-survival group. There was a significant difference in the use of definitive antibiotics between the survival and non-survival groups ($p < 0.001$); the survival group used a higher number of definitive antibiotics compared to the non-survival group.

Using multivariate logistic regression analysis adjusted for possible confounders (age and gender variables) (Table 3), being prescribed two or more definitive antibiotics (OR = 0.075, 95% CI = 0.017–0.340, $p = 0.001$) and ipratropium/salbutamol (OR = 0.140, 95% CI = 0.028–0.705, $p = 0.017$) were independently associated with lower mortality.

Table 4 shows the results of antibiotic susceptibility assay for MDR-AB isolates. The strains were tested against different types of antibiotics. They had variable resistance to different antibiotics. No strain was sensitive to ceftriaxone, ciprofloxacin, pefloxacin, and ticarcillin/clavulanic acid, and only 0.9% of isolated strains were susceptible to imipenem. Colistin was the most active agent (100% sensitive) followed by tigecycline (50%).

Discussion

To the best of our knowledge, this is the first retrospective study to provide detailed epidemiologic data and to evaluate predictive factors of mortality among patients with VAP infected with MDR-AB. The results of our study reveal three main findings. First, the percentage of MDR-AB in our study was 98.3% of all VAP cases, which is higher than previously reported in VAP (20%–80.5%) [12,22,23] and other nosocomial infections (15.7%–75%) [10,24-26] in different countries. Second, independent predictors of 14-day mortality in MDR-AB VAP patients were an inadequate number of definitive therapies and not using nebulized

Table 4. Susceptibility assay of multidrug-resistant *A. baumannii* isolates.

Antibiotic	Percentage of isolates[a]		
	Sensitive	Intermediate	Resistant
Amikacin	16.4	6.6	77.0
Ampicillin	0.0	0.0	100
Ampicillin/sulbactam	7.7	7.7	84.6
Aztreonam	0.0	1.8	98.2
Cefepime	0.0	0.9	99.1
Ceftazidime	0.0	0.9	99.1
Ceftriaxone	0.0	0.0	100
Ciprofloxacin	0.0	0.0	100
Colistin	100	0.0	0.0
Gentamicin	2.7	5.3	92.0
Imipenem	0.9	1.7	97.4
Levofloxacin	0.0	0.0	100
Meropenem	1.8	0.0	98.2
Minocycline	17.7	28.4	54.0
Pefloxacin	0.0	0.0	100
Piperacillin	0.9	0.0	99.1
Piperacillin/Tazobactam	0.9	1.8	97.3
Rifampin	24.6	63.8	11.6
Tetracycline	2.6	5.1	92.3
Ticarcillin	1.5	0.0	98.5
Ticarcillin/clavulanic acid	0.0	0.0	100
Tigecycline	50.0	12.5	37.5
Tobramycin	29.1	2.7	68.2
Co-trimoxazole	25.2	0.0	74.8

[a] Percentage was considered as the tested antibiotics were different in different years.

ipratropium/salbutamol. Third, all VAP cases were susceptible to colistin in our institution.

Consistent with previous studies [11], an inadequate number of definitive treatments was identified as one of the independent factors associated with higher mortality in the present study. This finding supports the use of antibiotics to which bacteria are susceptible and supports the prescription of two or more of those antibiotics rather than empirical prescription. The use of two or more antibiotics has the potential to broaden the antibiotic spectrum, to exert additive or synergistic effects, and to reduce the possible emergence of resistant bacteria or superinfection. However, drug availability, adverse drug reactions, drug-drug interactions, and cost are also important factors that should be considered in drug selection [27].

Those patients who were prescribed ipratropium/salbutamol nebulizer treatment had lower mortality. This is a combined product of ipratropium bromide and salbutamol sulfate that acts on both muscarinic and beta2-adrenergic receptors, respectively, in the lungs, leading to bronchodilation. Most patients on MV have respiratory failure, and this nebulizer improves air flow, relieves underlying inflammatory bronchospasm, and thus achieves better airway protection [28], which potentially could explain this association. Generally, this medication is used as supportive rather than curative therapy during MV to facilitate patient management [28]. More clinical studies are needed to explore the association between using a bronchodilator as adjunctive therapy and prognosis in MDR-AB infected cases.

In our VAP cases, the resistance rate for colistin in susceptibility assays was zero, and it was the most commonly used definitive treatment of choice. Colistin is an old drug that was infrequently used due to its nephrotoxicity and neurotoxicity. More recently, it has been revived as one of the last-resort therapies for MDR-AB infections [7,9,23]. In our institution, colistin cannot be used as empirical therapy due to inadequate evidence in the literature supporting its usage [29], and sometimes, it is not available for definitive therapy. A multicenter, randomized clinical trial in Europe that it is designed to investigate the efficacy and safety of colistin as empirical therapy in treating VAP due to Gram-negative bacilli is currently ongoing [30]. Meanwhile, empirical use of colistin (based on infectious disease consultation) may be justified in some institutions by high incidence rates of resistant pathogens [31,32]. Future studies to explore the association between using colistin as empirical treatment and prognosis in MDR-AB infected cases are needed.

Fluoroquinolones were the initial agents used most commonly in all VAP cases in our center, yet all *A. baumannii* isolates were resistant to fluoroquinolones. Current guidelines of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) for the management of VAP stress the clinical benefit of appropriate empirical therapy, which is defined as using initial antibiotics with *in vitro* activity against identified microorganisms causing infection [1]. Inadequate empirical therapy was reported to be associated with poor prognosis in patients with *A. baumannii* infection [11]. More targeted antibiotic therapy has the potential to improve clinical outcomes in patients with VAP [16].

This study had some limitations. First, it was retrospective and completed in a single tertiary care hospital setting. Second, it is unclear if mortality in this study was influenced by the patient's underlying condition rather than the actual mortality associated with MDR-AB VAP. Third, limited numbers of patients in each comparable group had the potential to restrict the ability to detect differences in the outcome of interest, leading to wide confidence intervals. Finally, we were unable to extract data on antibiotic dose or duration for any cases due to poor reporting. Therefore, the impact of antibiotic dose and duration on 14-day mortality is not known. Also, the effect of delay in starting antibiotic treatment is another factor to consider. This study was a preliminary and the findings exploratory. However, it is the largest study to provide detailed epidemiological data in this group of VAP patients with MDR-AB to date.

Conclusions

This study is unique in evaluating the predictors of mortality in monomicrobial VAP cases with MDR-AB. Our results suggest the incidence of MDR-AB VAP in critical care units is high and that prescription of antibiotics based on antibiotic susceptibility rather than empirical prescription and the use of bronchodilators is associated with lower mortality in this population All MDR-AB VAP cases were susceptible to colistin, illustrating its potential as a first-line treatment for this condition. Larger prospective studies are needed to explore whether these findings can be replicated in different clinical settings.

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Authors' contributions

BA and FM designed the study. RG and FM were responsible for the acquisition of data.
BA, AM, RG, and SS analyzed and interpreted the data. BA, AM, and SS wrote the manuscript.

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