

Defining the Risk Factors for the Evolution of Pan-Drug Resistance (PDR) *Acinetobacter Baumannii* Infections in Intensive Care Units

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Abstract

Aim: *Acinetobacter baumannii* is one important nosocomial pathogens. *Acinetobacter* infections causes long in hospital stay, mortality and morbidity. The aim of this study is to define the risk factors of PDR *A. baumannii* caused health care related (HCR) infections.

Methods: In the study of Cumhuriyet University Hospital between 01.01.2012-31.12.2013 is a case-control study was performed retrospectively. 49 PDR *A. baumannii* caused ventilator associated pneumonia and bacteremia, 71 other bacteria caused ventilator associated pneumonia and bacteremia patients were involved in this study. The PDR *A. baumannii* infection observed cases and the cases irrelevant to PDR *A. baumannii* infections are compared in terms of risk factors.

Results: As a result of the Univariate Analysis, it was found that DM, traumas, CCI>4, steroid use, hospitalization history in the last 3 months, and antibiotic use in the last 3 months were statistically and significantly higher in the PDR *A. baumannii* Group. Multivariate analysis was used to determine the risk factors with a p value of 0.1 and below by univariate analysis. In this respect, traumas (OR=93.32, p=0.011), steroid use (OR=21.09, p<0.001) and antibiotic use in the last 3 months. (OR=26.97, p=0.001) were determined as independent risk factors in the development of PDR *A. baumannii* VAP and bloodstream infection.

Conclusions: All risk factors for health care related PDR. *Acinetobacter* infections were modifiable. The control of these factors may decrease the ratio of PDR *A. baumannii*. In case of detection of PDR *A. baumannii* infection in hospitals, control measures should be applied, hospital staff should be educated and inappropriate antibiotic use should be prohibited.

Keywords: PDR, *Acinetobacter baumannii*, risk factors, control precautions

1. Introduction

Due to its improved environmental resistance, *Acinetobacter baumannii*, a non-fermentative Gram-negative coccobacillus, has gained more notoriety as a pathogen in healthcare settings.¹ *A. baumannii* is thought to make up 4%–7% of ventilator-associated pneumonia (VAP) and 1%–2% of nosocomial bloodstream infections.²⁻⁵ According to epidemiological research, the death rates of infections caused by *A. baumannii* range from 7.8% to 23% outside of intensive care units (ICUs) and from 10% to 43% in ICUs,

which has greatly raised the infirmity's expenses.⁶ According to studies, there are clear patterns in the distribution of departments where pan-resistant *Acinetobacter baumannii* infections occur, with ICUs having one of the highest infection rates.⁷⁻⁸ For instance, ICU patients have undergone more invasive procedures in addition to being severely ill. The vast majority of patients have also taken a combination of a lot of different broad-spectrum antibiotics, which weakens their body's defenses and makes it easier for them to contract hospital infections. The current strain of pan-resistant *Acinetobacter baumannii* can result in infections of the blood, urinary tract, central nervous system, lungs and abdomen. Pulmonary infection is one of the most prevalent.⁹⁻¹⁰

According to some studies, the host's health, prior antimicrobial drug exposure (especially broad-spectrum antibiotics), prior colonization with *A. baumannii*, increased Pitt bacteremia score, being in the intensive care unit, and recent invasive procedures are risk factors associated with the acquisition of pan drug resistant (PDR) in A

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baumannii bacteremia.¹¹⁻¹³ Old age, neutropenia, malignancy, surgery prior to bacteremia, post-transplantation, severity of illness as determined by Pitt bacteremia score or Acute Physiology and Chronic Health Evaluation II score, ICU stay, having a lower level of albumin, respiratory tract as the origin of bacteremia, and inappropriate initial antimicrobial therapy are risk factors of mortality of *A. baumannii* bacteremia that have been reported in various parts of the world in recent years.¹⁴⁻¹⁶

All patients who were treated in intensive care units and who developed VAP and bloodstream infections, which are the most common PDR *Acinetobacter* infections, were included in this study. Two groups were formed as infections caused by PDR *A. baumannii* and infections caused by other bacterial agents, and it was aimed to determine the risk factors for VAP and bloodstream infection caused by PDR *A. baumannii*.

2. Materials and methods

2.1. Objective

The patients who were treated in ICUs, had high mortality and developed the most common PDR (Pan Drug Resistance) *Acinetobacter* infections VAP (Ventilator Associated Pneumonia) and bloodstream infections were included in the present study, and the risk factors for the development of PDR *A. baumannii* infection were aimed to be determined.

2.2. Patient Population

Cumhuriyet University Medical Faculty Hospital is a tertiary healthcare institution that serves in all branches with a bed capacity of 1150. Anesthesia ICU provides intensive care service with a bed capacity of 25. Patients receiving inpatient treatment at Cumhuriyet University Practice and Research Hospital are followed by the Infection Control Committee with the Active Surveillance Method. Daily surveillance continues until the patients are discharged from the Intensive Care Unit or until mortality, and patient information is recorded in the surveillance follow-up form. The names-surnames, ages, genders, hospitalization dates, hospitalization departments, clinical diagnoses, underlying diseases, risk factors, operations, interventions, hospital infection diagnoses, antibiotics used, reproducing agents, and susceptibility to antibiotics of patients are recorded in the surveillance follow-up form.

2.3. Definitions

The definitions of hospital-acquired infections were made according to CDC (Centers for Disease Control and Prevention) criteria in the present study (56). Among the patients who were hospitalized and who developed nosocomial infections (VAP and bloodstream infections) during the study period, the cases with PDR *Acinetobacter* Infection were included as the Case Group, and infections with other bacteria than PDR *Acinetobacter* were included as the Control Group.

2.4. Data Collection and Microbiological Analysis:

The patient files were examined from the registry system in the Cumhuriyet University Practice and Research Hospital Infection Control Committee Surveillance System, Hospital Automation System, and patient archive files. In this respect, the clinical and microbiological data of the patients who were hospitalized in the Anesthesia ICU between 01/01/2012 and 31/12/2013 in lower respiratory tract samples (deep tracheal aspirate and endotracheal aspirate) and blood cultures with VAP and bloodstream infections caused by other bacteria than *A. baumannii* were evaluated retrospectively. Patients were followed up with visits by an infectious diseases specialist. Adult patients who were over 18 years of age were included in the study. Healthcare and ventilator-associated pneumonia and bloodstream infection caused by *A. baumannii* and non-*A. baumannii* bacteria were evaluated in each patient. In cases with more than one infection episode, those with one single episode

were included in the study. Patient information was recorded in the form obtained by scanning previous literature. The patients' names-surnames, ages, genders, dates of follow-ups, hospitalizations, history of hospitalization in the last 3 months, Glasgow Coma Score, APACHE 2 (Acute Physiology And Chronic Health Evaluation) scores, SOFA (Sequential Organ Failure Assessment) Scores, and CCI (Carlson Comorbidity Index scores), underlying diseases, invasive procedures, antibiotic use in the last 3 months, the day of infection, the sites of infections and reproduction sites of bacteria, laboratory values, radiological imaging results, initial treatments, mortality status, and antibiotic susceptibility were included in the form.

The cases with PDR *Acinetobacter* infection and infections with non-*Acinetobacter* bacteria were compared in terms of risk factors. Lower respiratory tract samples were diluted 1/10 and inoculated at Columbia Agar 5% sheep-blood (Salubris) and Eosin Methylene Blue (EMB) Agar (Salubris) media with 0.01 ml diameter sterile cells and incubated at 35.5-37.5°C for 24-48 hours. The colonies >10 over 6 on Columbia Agar and EMB Agar Media were considered significant and were taken to Phoenix NMIC ID/82 Panels (Mc Farland 0.5) within the framework of the manufacturer's operating instructions and in line with the Clinical and Laboratory Standards Institute (CLSI) recommendations. The identifications were then made with the BD Phoenix 100 (BD Diagnostic Instrument Systems USA) and antimicrobial susceptibilities were determined. Blood cultures were evaluated with the BACTEC 9120 Automated System (BD Diagnostic Instrument Systems USA). Control passage was performed for those who did not have a growth signal for 5 days. The samples with a growth signal were added to Columbia Agar 5% sheep blood (Salubris) and Eosin Methylene Blue (EMB) Agar (Salubris) Media and were incubated for 24-48 hours at 35.5-37.5°C. Growing samples were taken to Phoenix NMIC ID/82 Panels (Mc Farland 0.5) within the framework of the manufacturer's instructions and in line with the Clinical and Laboratory Standards Institute (CLSI) recommendations. The identification was then made with the BD Phoenix 100 (BD Diagnostic Instrument Systems USA) and antimicrobial susceptibility was determined. The data reported with these definitions were obtained from the Registry System of the Cumhuriyet University Practice and Research Hospital Infection Control Committee Surveillance System.

2.5. Statistical Analysis:

The data obtained in the present study were loaded into the SPSS 14.0 (Statistical Package for Social Sciences) program, and the significance test of the difference between two means in independent groups and the Chi-Square Test was used in the evaluation of the data. In cases where the assumptions about the Fisher Exact Chi-Square Test could not be fulfilled, the Fisher Exact Chi-Square Test was used to calculate the Chi-Square Value with the Monto Carlo Method. Multivariate Logistic Regression Analysis was used to determine the risk factors and the error level was taken as 0.05.

3. Results

The mean age of the patients who were included in the study was found to be 69.8±SD15.0 years and no significant differences were detected between the groups in terms of age and gender.

The most frequent hospitalization diagnoses of the cases were infection and respiratory failure. Trauma, Systemic Vascular Disease (SVD), Acute Kidney Injury (AKI), surgery, and immunosuppressive treatment were other less frequent diagnoses.

At least one underlying disease that might affect mortality and morbidity was detected in 99 of the patients in the Study Group. The most common diseases were Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), and Hypertension (HT). In the

PDR *A. baumannii* VAP and bacteremia group, 22 (50%) of the patients had DM, and 19 (26.8%) of the patients in the control group had DM. The frequency of DM was found to be statistically and significantly higher in the PDR *A. baumannii* Group ($p=0.013$). Similarly, when the groups were evaluated in terms of traumas, the frequency of traumas was found to be statistically higher in the group in which PDR *A. baumannii* was the causative agent ($p=0.011$).

The Carlson Comorbidity Score (CCI) rate was found to be ≤ 4 in 52 (46%) in the patients in the Study Group, and the CCI rate was >4 in 61 patients (54%). The CCI score was ≤ 4 in 14 (33.3%) in the PDR *A. baumannii* VIP and Bacteremia Group, and 28 (66.7%) of them had scores above 4. In the control group, 38 (53.5%) of the patients had a CCI score of 4 or lower, and 33 (46.5%) had a CCI score above 4. A statistically significant CCI score greater than 4 was detected in the PDR *A. baumannii* Group as the risk factor ($p=0.037$).

Steroid use at a dose that would cause immunosuppression was detected in 35 (31%) of the patients in the Study Group and steroid use was not detected in 78 (69%) patients. In the PDR *A. baumannii* VAP and Bacteremia Group, 26 (61.9%) patients had steroid use, and 16 (38.1%) did not use steroids. In the control group, 9 (12.7%) patients were using steroids and 62 (87.3%) were not using. When the groups were evaluated based on the statistical analysis, steroid use was found to be higher in the group in which PDR *A. baumannii* was the causative agent ($p<0.001$).

No significant differences were detected in the comparison of the Study and Control Group patients in terms of invasive interventions.

Significant differences were detected between the groups in terms of hospitalization in the last 3 months, antibiotic use in the

last 3 months, and infection occurring 30 days after hospitalization.

As a result of the Univariate Analysis, it was found that DM, traumas, CCI >4 , steroid use, hospitalization history in the last 3 months, and antibiotic use in the last 3 months were statistically and significantly higher in the PDR *A. baumannii* Group.

Multivariate analysis was used to determine the risk factors with a p value of 0.1 and below by univariate analysis. In this respect, traumas (OR=93.32, $p=0.011$), steroid use (OR=21.09, $p<0.001$) and antibiotic use in the last 3 months (OR=26.97, $p=0.001$) were determined as independent risk factors in the development of PDR *A. baumannii* VAP and bloodstream infection.

Antibiotic use in the last 3 months (Ampicillin-Sulbactam, 2nd and 3rd-generation Cephalosporin, Quinolone, Piperacillin-Tazobactam, Carbapenem, or Glycopeptide) was found to be statistically and significantly higher when the groups were compared.

As a result of the comparisons of the clinical and laboratory results between the groups, no significant differences were detected between the clinical and laboratory results.

Table 2

Independent risk factors for the development of PDR *A. baumannii* VAP and Bloodstream infections (multivariate logistic regression analysis)

Variable	Coefficient	SE	P value	Odds ratio	%95 CI
Trauma	4.54	1.79	0.011	93.32	(2.8-3110.4)
Steroid use	3.05	0.73	<0.0001	21.09	(5.09-87.44)
Use of antibiotics in the last 3 months	3.29	0.99	0.001	26.97	(3.82-190.4)
Constant	-14.22	4.48	0.002	0.000	

SE, standart error ; CI(confidence interval)

Table 3

Comparison of antibiotic use in study and control group patients

Variables	PDR <i>A. baumannii</i> VAP and bacteremia N:42(%)	Control group VAP and bacteremia N:71(%)	Total patients N:113(%)	P value
Antibiotic used				
Ampicillin sulbactam	28(66.7)	17(23.9)	45(39.8)	0.001
Cephalosporins	17(40.5)	10(14.1)	27(23.9)	0.001
Aminoglycosides	3(7.1)	3(4.2)	6(5.3)	0.669
Quinolones	9(21.4)	2(2.8)	11(9.7)	0.002
Piperacillin tazobactam	23(54.8)	6(8.5)	29(25.7)	0.001
Carbapenems	13(31)	4(5.6)	17(15)	0.001
Glycopeptides	10(23.8)	2(2.8)	12(10.6)	0.001
Linezolid	2(4.8)	-	2(1.8)	0.136
Colistin	-	-	-	-
Metronidazole	3(7.1)	1(1.4)	4(3.5)	0.144

4. Discussions

Patients hospitalized in ICUs have a higher risk of NI because of complex problems such as low immune status, comorbid diseases (e.g., cancer, burns, diabetes), and invasive device applications that disrupt body integrity.¹⁷ Studies have been conducted for many years to evaluate the risk factors and their effects on mortality in

Table 1

Significant findings as a result of the comparison of the demographic and clinical characteristics of the study and control group patients

Variables	PDR <i>A. baumannii</i> VAP and bacteremia N:42(%)	Control group VAP ve bacteremia N:71(%)	Total patients N:113(%)	P value
Comorbid Diseases				
•Diabetes mellitus	21(50)	19(26.8)	40(35.4)	0.013
•COPD	29(69)	39(54.9)	68(60.2)	0.138
•Hypertension	26(61.9)	46(64.8)	72(63.7)	0.758
•Trauma	5(11.9)	1(1.4)	6(5.3)	0.026
CCI				
• ≤ 4	14(33.3)	38(53.5)	52(46)	0.037
• >4	28(66.7)	33(46.5)	61(54)	
History of hospitalization in the last 3 months				
•Yes	27(64.3)	22(31)	49(43.4)	0.001
•No	15(35.7)	49(60)	64(56.6)	
Day of hospitalization for infection				
• ≤ 30 day	23(54.8)	58(81.7)	58(81.7)	0.004
• >30 day	19(45.2)	13(18.3)	13(18.3)	
Use of antibiotics in the last 3 months				
•Yes	39(92.9)	32(45.1)	71(62.8)	0.001
Steroid use				
•Yes	26(61.9)	9(12.7)	35(31)	0,001
•No	16(38.1)	62(87.3)	78(69)	

infections caused by *A. baumannii* and different results were reported. The present study examined the effects of bacteremia and pneumonia caused by *A. baumannii* on risk factors and mortality with univariate and multivariate analyses and the independent risk factors.

Comorbid diseases prolong the length of stay in hospitals and intensive care units and increase the frequency of invasive interventions. In a previous study, Diabetes Mellitus was found to be a risk factor in the formation of infection with *A. baumannii* in terms of underlying diseases.¹⁸ Similarly, in the present study, PDR (Pan Drug Resistance) *A. baumannii* was found to be a Diabetes Mellitus risk factor in the VAP (Ventilator-Associated Pneumonia) and Bacteremia Group.

The relationship between traumatic events and the development of Nosocomial Infections is associated with increasing injury severity scores of the patients.¹⁹ It is also considered that trauma results in neutrophil dysfunction, which leads to decreased immune response and Nosocomial Infections.²⁰ In the study conducted by Bergogne-Berezin et al., trauma was identified as a risk factor for infection with *A. baumannii*.²¹ In the present study, traumas were evaluated in the group of underlying diseases, and similarly, PDR *A. baumannii* was identified as a risk factor in the VAP and Bacteremia Group.

The CCI score is calculated based on the underlying diseases and age. Various risk factors are frequently investigated in Nosocomial Infections caused by *Acinetobacter baumannii*. Age, gender, length of hospital stay, length of stay in the Intensive Care Unit, co-morbidities, invasive interventions, and antibiotics given to patients were identified as risk factors in previous studies.²²⁻²³⁻²⁴ In the present study, CCI (Carlson Comorbidity Score) was determined as a risk factor in the occurrence of PDR *A. baumannii* infection.

It is now known that secondary infections can occur in patients who use steroids. In the study that increased the risk of infection with *A. baumannii* in patients using ≥ 1 mg/kg/day steroids, the patients were exposed to steroids according to their underlying diseases.¹⁸ Similarly, PDR *A. baumannii* infection was found to be a risk factor in patients using steroids in the present study.

Exposure to colonization and interventional procedures increases in patients who are hospitalized in the last 3 months. For this reason, hospitalization in the last 3 months was found to be an important risk factor for PDR *A. baumannii* infection in a previous study.²⁵ In the present study, the history of previous hospitalization was found as a risk factor.

Antibiotic use was previously recognized as a risk factor for multidrug-resistant gram-negative infections.²⁶ Previous studies reported that frequent use of Carbapenem, third-generation Cephalosporins, Quinolones, and Aminoglycosides are risk factors for *Acinetobacter* colonization infection.²⁷⁻²⁸⁻²⁹ Ampicillin Sulbactam, 2nd and 3rd-generation Cephalosporins, Quinolones, Piperacillin Tazobactam, Carbapenem, and Glycopeptide Antibiotics were identified as risk factors in the present study, similar to other studies.

In the statistical analysis made to compare the day of hospitalization in the formation of infection, the infection occurred after 30 days in the group with PDR *A. baumannii* infection and was determined as a risk factor. The emergence of nosocomial antibiotic-resistant pathogens increases with each day of hospitalization. The longer the hospital stay, the longer the contact with contaminated floors and equipment. In their study, Tunay et al. reported that the duration of hospital stay was determined as a risk factor for the formation of PDR *A. baumannii*.²⁹

A. baumannii strains have become resistant to many antimicrobial agents, especially in recent years, which has caused a limited number of antimicrobial agents to remain against *Acinetobacter* infections.³⁰

Univariate analysis was used in the present study to determine the risk factors with a *p*-value of 0.1 and below to determine the independent risk factors, and multivariate analysis was used for this purpose. Traumas, steroid, and antibiotic use in the last 3 months were determined as independent risk factors for the development of PDR *Acinetobacter baumannii* VAP and bloodstream infections.

In recent studies, conditions such as underlying diseases, antibiotic use, and invasive procedures continue to be risk factors for *Acinetobacter baumannii*.³¹⁻³²

5. Conclusions

In conclusion, when the results obtained in the present study were evaluated, VAP and bacteremia are frequently detected in wards such as ICUs with many underlying diseases and where more than one invasive intervention is applied. This shows that infection control procedures must be applied strictly in these wards and units. We think that it is important, especially in terms of ensuring the continuity of infection control training for the staff working in these units, reducing the transmission of bacteria between patients, between staff and patients, between equipment and patients, and between staff and between units. The importance of antibiotic use in these patients with multiple comorbidities and invasive procedures has been shown once again.

It is important to have information on the risk factors in the development of infection with *Acinetobacter baumannii* and to follow these patients closely in terms of early detection.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Cumhuriyet University Faculty of Medicine Ethics Committee.

<https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=veDPLuExfG-pX23kTNj-9Q&no=SkmqQaBcD2WcW8e5my-XUg>

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