

## Risk Factors For Nosocomial Pan Drug Resistant Acinetobacter Baumannii Infections

Hastane Kaynaklı Pan Drug Resistant Acinetobacter Baumannii Enfeksiyonlarında Risk Faktörleri

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### ABSTRACT

**Aim:** Acinetobacter baumannii is an important nosocomial pathogen. The purpose of this study was to identify risk factors and mortality of nosocomial infections caused by pan drug resistant (PDR) Acinetobacter baumannii and to characterize their effects on mortality.

**Patients and Methods:** This study was performed at the Afyon Kocatepe University Faculty of Medicine. Nosocomial infections were defined according to the American Center for Disease Control (CDC). Patients with nosocomial infections caused by Acinetobacter baumannii were included in the study. Patients identified as PDR Acinetobacter baumannii and non-PDR Acinetobacter baumannii infection were compared in terms of risk factors.

**Results:** Two different groups were constructed, one group consisting of 145 PDR and the other of 145 non-PDR Acinetobacter baumannii cases. Stay history in an internal intensive care unit (p=0.001), their duration of hospital stay (p=0.031), renal disease (p=0.003), mechanical ventilation (p=0.001), prior usage history of carbapenem (p=0.001), presence of nosocomial pneumonia (p=0.001), were independent risk factors associated with PDR Acinetobacter baumannii infections. The mortality rate for the PDR group was 61.8% and it was 38.2% in the non-PDR group (p=0.008).

**Conclusion:** PDR Acinetobacter baumannii infections are important nosocomial infections with a high mortality rate. Patients' carbapenem usage, stay history in an internal intensive care unit, renal comorbid diseases, and a diagnosis of nosocomial pneumonia are important risk factors for PDR Acinetobacter baumannii infections. In nosocomial infections caused by PDR Acinetobacter baumannii, many risk factors were modifiable.

Keywords: Acinetobacter baumannii, antibiotic resistance, antimicrobial therapy.

### ÖZ

**Amaç:** Acinetobacter baumannii, önemli nozokomiyal bir patojendir. Bu çalışmanın amacı, pan drug resistant (PDR) Acinetobacter baumannii nedenli nosokomiyal enfeksiyonlar için risk faktörlerinin ve mortalite üzerine olan etkinin tanımlanmasıdır.

**Hastalar ve Yöntemler:** Çalışma Afyon Kocatepe Üniversitesi Tıp Fakültesi'nde gerçekleştirilmiştir. Amerikan Hastalık Kontrol Merkezi (CDC) tanı kriterlerine göre tanımlanmıştır. Acinetobacter baumannii nedenli nozokomiyal enfeksiyon tanımlanan hastalar çalışmaya dahil edilmiştir. PDR Acinetobacter baumannii ve non-PDR Acinetobacter baumannii enfeksiyonu saptanan olgular risk faktörleri yönünden karşılaştırılmıştır

**Bulgular:** Biri 145 PDR diğeri 145 PDR olmayan Acinetobacter baumannii vakalarından oluşan iki farklı grup oluşturuldu. Dahili yoğun bakım ünitesinde yatış öyküsü (p=0,001), hastanede kalış süresi PDR grupta ortalama 28,2±23,0 (p=0,031), renal hastalık (p=0,003), mekanik ventilasyon (p=0,001), önceden karbapenem kullanma öyküsü (p=0,001), nozokomiyal pnömoni varlığı, (p=0,001) bağımsız risk faktörü olmuştur. Mortalite oranı PDR grupta % 61,8, non-PDR grupta % 38,2, olarak belirlenmiştir (p=0,008).

**Sonuç:** PDR Acinetobacter baumannii enfeksiyonları mortalite oranı yüksek önemli nozokomiyal enfeksiyonlardır. Dahili yoğun bakım ünitesinde yatış öyküsü, hastanede kalış süresi, renal hastalık, mekanik ventilasyon, karbapenem kullanım öyküsü, nozokomiyal pnömoni varlığı, solunum sekresyon örneği PDR Acinetobacter baumannii enfeksiyonu için önemli risk faktörleridir. PDR Acinetobacter baumannii nedenli nozokomiyal enfeksiyonlarda çoğu risk faktörleri düzeltilebilir özelliktedir.

Anahtar Kelimeler: Acinetobacter baumannii, antibiyotik direnci, antimikrobiyal tedavi.

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## INTRODUCTION

**A**cinetobacter baumannii is one of the main causes of nosocomial infections [1]. Due to its poor nutritional needs and stability in a range of environmental conditions, it can survive for weeks on abiotic surfaces. In the human body, it is located inside the normal bacterial flora of the skin, oral cavity, respiratory tract, and gastrointestinal system. Carriage in healthcare workers skin and environmental contaminations cause outbreaks [2,3,4]. Serious nosocomial infection outbreaks caused by this opportunistic pathogen include ventilator-associated pneumonia, bloodstream infections, urinary system infections, intracranial infections, and skin and soft tissue infections [5].

Since Acinetobacter baumannii has become highly resistance to antimicrobial medications in our country as well as all over the world, its treatment is troublesome, and it leads to many life-threatening hospital-acquired infections. Carbapenems are usually the antibiotics of choice for treating serious infections caused by Acinetobacter baumannii. However, reports of imipenem-resistant Acinetobacter baumannii strains have been steadily increasing over the past few years [6,7]. Due to the increased level of antimicrobial resistance in recent years, pan drug resistant (PDR) Acinetobacter baumannii infections are frequently encountered. MDR means resistant to three or more antimicrobial classes. Definitions in the literature for PDR vary. PDR is defined in gram-negative bacilli as resistant to all antibiotics except colistin, tigecycline and aminoglycosides (8). Many studies have examined the risk factors of multidrug-resistant Acinetobacter baumannii infections. As distinct from previous studies, the aim here is to evaluate the risk factors of PDR Acinetobacter baumannii infections and their mortality rates.

## PATIENTS AND METHODS

This retrospective case-control study was performed in the Afyon Kocatepe University Faculty of Medicine. The hospital is a tertiary-care hospital providing services in all branches. The hospital has a total of eight intensive care units; there are four medical (internal diseases, cardiology, neurology, and chest diseases) and four surgical intensive care units (cardiovascular surgery, general surgery, reanimation, and neurosurgery). Hospita-

lized patients are followed by the Infection Control Committee using the active surveillance method. Daily surveillance continues until the patients are either discharged from the intensive care unit or they are exitus. Patients' information is recorded on surveillance forms. The study was conducted in accordance with the principles of the Declaration of Helsinki.

In this study, nosocomial infections were defined according to the American Center for Disease Control (CDC) criteria [9]. The study (retrospective case-control) was performed at the Afyon Kocatepe University Faculty of Medicine, from July 1st, 2005 to March 1st, 2012. Patients who were diagnosed with infections caused by Acinetobacter baumannii after 48 hours of hospital stay were included in the study as case and control groups. Patients determined to have PDR Acinetobacter baumannii infections were categorized as being in the case group, and those determined to have non-PDR Acinetobacter baumannii infections were in the control group. PDR Acinetobacter baumannii infection-detected cases were compared to the non-PDR Acinetobacter baumannii infection-detected cases with respect to risk factors.

Patients' information from the surveillance forms was analyzed. Accordingly, clinical and microbiological data of those patients who had Acinetobacter baumannii growth in sterile area cultures were evaluated retrospectively. Adult patients over 18 years of age were included in this study. Infections caused by Acinetobacter baumannii were evaluated for each patient. For patients who had more than one infection episode, only one episode was considered. For the two patient groups which are isolated Acinetobacter baumannii patients' demographic information (such as age and gender), duration of hospital stay, units where they received treatment (internal intensive care, surgical intensive care, and non-intensive care units), surgical procedures, underlying systemic diseases, invasive medical procedures (central venous catheter, urinary catheter, mechanical ventilation, nasogastric tube, thorax tube, colostomy), antibiotic usage and variability, infection types, antibiotic susceptibility, and the presence of mortality were recorded. Prior antibiotic exposure was defined as at least 48 hours of therapy before isolation of the Acinetobacter baumannii. Mortality associated

with infection was defined as the infection's mortality occurring within the planned standard duration of therapy.

Bacteria identifications were performed by the Afyon Kocatepe University Faculty of Medicine, Medical Microbiology Laboratory with VITEC2 (BioMerieux, France). Data reported for these identifications were obtained from the register system within the constitution of the Afyon Kocatepe University Faculty of Medicine's Infection Control Committee Surveillance system.

All of the patient data were recorded in SPSS 18.0 for Windows for analysis. Features of the case and control groups were compared using the Chi-square test for two variables and the Mann-Whitney U test for continuous variables. The significance level was  $p < 0.05$ .

## RESULTS

During the study period, Acinetobacter baumannii infections were detected in 290 patients. Two different groups were constructed, one group consisting of 145 PDR and the other of 145 non-PDR Acinetobacter baumannii cases.

When infection types were examined, the most frequent type was nosocomial pneumonia (n: 92, 63.4%) in the PDR group, while other detected infections were nosocomial bloodstream infections (n: 23, 15.9%), urinary system infections (n: 8, 5.5%), and soft tissue infections (n: 7, 4.8%) (see Table 1). A meaningful statistical relationship between nosocomial pneumonia and PDR Acinetobacter baumannii infections was determined ( $p = 0.001$ ).

Until Acinetobacter baumannii isolation, the duration of hospital stay for the PDR group was found to be longer (for the non-PDR group, it was an average of  $24.0 \pm 19.3$  days and for the PDR group,  $28.2 \pm 23.0$  days). A meaningful statistical relationship between duration of hospital stay and PDR Acinetobacter baumannii infections was determined ( $p = 0.031$ ).

When the distribution of infections caused by Acinetobacter baumannii with respect to hospital units was examined, 21 non-PDR infections (14.5%) in the control group and 46 PDR Acinetobacter baumannii infections (31.7%) in the case

group were identified as occurring in the internal intensive care units. A higher stay rate was detected for the PDR group than the Non-PDR group in internal intensive care units ( $p = 0.00$ ).

When evaluated in terms of patients' comorbid diseases and applied medical procedures, a meaningful statistical relationship was found between renal diseases ( $p = 0.003$ ), mechanical ventilation applications ( $p = 0.001$ ), and PDR Acinetobacter baumannii infections.

Patients' general features and a single variable analysis of risk factors are shown in Table 2. Patients' duration of hospital stay, history of stay in an internal intensive care unit, renal comorbid diseases, and mechanical ventilation applications were significant risk factors for PDR Acinetobacter baumannii infections.

Table-1 Infection Type Risk Analysis

Infection Type	Pan Drug Resistant (%)	Non-Pan Drug Resistant (%)	Odds Rate(- CI)	P value*
Nosocomial Pneumonia	92 (%63,4)	55 (% 37,9)	2,84 (1,76-4,57)	0,001
Blood Stream Infection	23 (%15,9)	61 (% 42,1)	3,85 (2,21-6,70)	0,001
Urinary System Infections	8 (% 5,5)	7 (% 4,8)	0,86 (0,30-2,46)	0,791
Surgery Area Infection	15 (%10,3)	19 (% 13,1)	1,30 (0,63-2,68)	0,465
Soft Tissue Infection	7 (% 4,8)	3 (% 2,1)	0,41 (0,10-1,64)	0,198

\* $p < 0,05$  was accepted as reasonable.

When patients' prior antibiotic usage was analyzed, carbapenem usage was detected in 42 patients (29.0%) in the non-PDR group and in 69 patients (47.6%) in the PDR group. An analysis of the association between PDR infections and prior antibiotic usage thus indicated a reasonable relationship between carbapenem usage and PDR Acinetobacter baumannii infections ( $p = 0.001$ ). The case and control groups prior antibiotic usage and diversity are described in Table 3.

The mortality rate for the PDR group was 61.8% and it was 38.2% for the non-PDR group. A meaningful statistical relationship between mortality rate and PDR was found ( $p = 0.008$ ).

Table-2 Univariate Analysis of General Features and Risk Factors

Risk Factors	Pan Drug Resistant (%)	Non-Pan Drug Resistant (%)	Odds rate (CI)	P value*
Female	43 (%29,7)	50 (%65,5)		0,378
Male	102(%70,3)	95 (%34,5)		0,378
Average of Age (Year)	62,9 ± 17,3*	59,1 ± 19,1*		0,110
Duration of Hospital Stay (Year)	28,2 ± 23,2*	24,0 ± 19,3*		0,031
Stay in Internal Intensive Care Unit	46 (% 31,7)	21 (%14,5)	2,74(1,53-4,89)	0,001
Stay in Surgical Intensive Care Unit	68 (% 46,9)	90 (%62,1)	0,54(0,33-0,86)	0,009
Surgery Procedure	70 (% 48,3)	78 (%53,8)	0,80(0,50-1,27)	0,347
Underlying Diseases				
Cardiovascular System Disease	18 (%12,4)	26 (%17,9)	0,64 (0,76-1,24)	0,190
Renal Disease	27 (%18,6)	10 (%6,9)	3,08 (1,43-6,64)	0,003
Neurologic Disease	38 (%26,2)	45 (%31,0)	0,78 (0,47-1,31)	0,363
Diabetes Mellitus	33 (%22,8)	29 (%20,0)	1,17 (0,67-2,06)	0,567
Hypertension	17 (%11,7)	38 (%26,2)	0,37 (0,20-0,70)	0,002
Respiratory Disease	43 (%29,7)	36 (%24,8)	1,27 (0,76-2,14)	0,356
Trauma	28 (%19,3)	31 (%21,4)	0,88 (0,49-1,56)	0,662
Malignancy	14 (% 9,7)	16 (%11,0)	0,86 (0,40-1,83)	0,700
Medical Interventions				
Central Venous Catheter	106 (%73,1)	109(%75,2)	0,89 (0,53-1,51)	0,687
Mechanical Ventilation	138 (%95,2)	106(%73,1)	7,25(3,12-16,85)	0,001
Urinary Catheter	132 (%91,0)	136(%93,8)	0,67 (0,27-1,62)	0,375
Tracheostomy	52 (%35,9)	41 (%28,3)	0,70 (0,42-1,15)	0,166
Nasogastric Drainage	38 (%26,2)	68 (%46,9)	0,40 (0,24-0,65)	0,001
Colostomy	10 (%6,9)	10 (%6,9)	1,00 (0,40-2,48)	1,000
Hemodialysis	9 (%6,2)	6 (%4,1)	1,53 (0,53-4,42)	0,426
Thorax Tube	10 (%6,9)	16 (%11,0)	0,59 (0,26-1,36)	0,217

\*p&lt;0,05 was accepted as reasonable.

Table-3 Univariate analysis of Antimicrobial Use

Antibiotic	Pan Drug Resistant (%)	Non-Pan Drug Resistant (%)	Odds Rate (CI)	P value*
Ampicillin-sulbactam	36 (% 24,8)	36 (% 24,8)	1,00 (0,58-1,70)	1,000
Aminoglycoside	15 (% 10,3)	49 (% 33,8)	0,22 (0,12-0,42)	0,001
First Generation Cephalosporin	13 (% 9,0)	13 (% 9,0)	1,00 (0,44-2,23)	1,000
Second Generation Cephalosporin	1 (% 0,7)	0 (% 0,0)	2,00 (1,78-2,25)	0,316
Third Generation Cephalosporin	31 (% 21,4)	66 (% 45,5)	0,32 (0,19-0,54)	0,001
Fourth Generation Cephalosporin	6 (% 4,1)	4 (% 2,8)	1,52 (0,42-5,50)	0,520
Carbapenem	69 (% 47,6)	42 (% 29,0)	2,22 (1,37-3,61)	0,001
Quinolone	40 (% 27,6)	45 (% 31,0)	0,84 (0,51-1,40)	0,519
Piperacillin-tazobactam	29 (% 20,0)	19 (% 13,1)	1,65 (0,88-3,11)	0,114
Cefoperazone-sulbactam	37 (% 25,5)	35 (% 29,1)	1,07 (0,63-1,83)	0,786
Glycopeptide	41 (% 28,3)	41 (%28,3)	1,00 (0,60-1,66)	1,000
Linezolid	22 (% 15,2)	22 (% 15,2)	1,00 (0,52-1,90)	1,000
Tigecycline	4 (% 2,8)	0 (% 0,0)	2,02 (1,80-2,28)	0,122
Colistin	1 (% 0,7)	1 (% 0,7)	1,00(0,06-16,14)	1,000
Antifungal	12 (% 8,3)	14 (% 9,7)	0,84 (0,37-1,89)	0,681

\*p&lt;0,05 was accepted as reasonable.

## DISCUSSION

In recent years, there has been an increased rate of infections caused by *Acinetobacter baumannii*, which is a gram negative non-fermentative bacterium. In our country, the *Acinetobacter baumannii* infection rate between 2004 and 2010 increased from 5.8% to 76.6% [10]. The most frequent localization and colonization place of nosocomial *Acinetobacter baumannii* is in the respiratory tract. In the EPIC II study, it was reported that 64% of 13,796 adult patients had respiratory *Acinetobacter baumannii* infections [11]. As in other studies, the most frequently encountered infection in the PDR group in our study was also nosocomial pneumonia (n: 92, 63.4%). When patients infected with PDR *Acinetobacter baumannii* were compared to non-infected patients, nosocomial pneumonia (63.4%,  $p=0.003$ ) was observed and mechanical ventilation (95.2%,  $p=0.001$ ) was needed more frequently in infected patients.

In nosocomial infections caused by *Acinetobacter baumannii*, various risk factors have been frequently researched. The risk factors that have been studied are age, gender, duration of hospital stay, stay in intensive care units, comorbid diseases, invasive procedures, and antibiotics given to the patients [7,8,12,13].

The length of hospital stay promotes *Acinetobacter baumannii* species colonization, invasive procedures, and antibiotic usage [1,5,14]. When risk factors for infections associated with resistant *Acinetobacter baumannii* were examined, the length of hospital stay was found to be a significant risk factor [7,15]. Similarly, in our study, the length of hospital stay was found to be the most significant risk factor for the development of infections.

Mortality, morbidity, and cost of intensive care infections are high [1]. Previous researchers studying *Acinetobacter baumannii* infections have found intensive care stay to be an important risk factor [5,7,15]. In our study, internal intensive care unit stay was a risk factor for PDR *Acinetobacter baumannii* infections ( $p=0.001$ ). We suggest that this results from features like immunosuppression for patients who have chronic diseases and serious physiological problems, an increased number of invasive procedures, and conditions requiring intensive care.

Comorbid diseases extend patients' stay in hospitals and intensive care units and increase their frequency of invasive procedures. They also pose a risk for *Acinetobacter baumannii* infections with the increased rate of nosocomial infections and the increased need for broad spectrum antibiotics. In prior research on patients with infections related to *Acinetobacter baumannii*, various underlying diseases have been detected, and when evaluated separately, no specific risk factors have been found [6,15]. In one study on the survival rate of patients with *Acinetobacter baumannii* infections, when underlying diseases were examined, hematologic malignancy and diabetes mellitus were found to be meaningful, and these patients had an increased mortality rate [16]. But in our study, distinct from previous studies, a meaningful statistical relationship was identified between renal diseases resulting from underlying diseases and PDR *Acinetobacter baumannii* infections ( $p=0.003$ ). Possible reasons for this include chronic renal failure in many patients who have renal diseases, longer hospital stays, and immunosuppression. Moreover, the majority of patients who are followed in internal intensive care units are chronic renal failure patients, and there is a dense patient population in hospital dialysis centers.

Prolonged broad spectrum antimicrobial treatment removes the normal flora and leads to the selection of resistant microorganisms like *Acinetobacter baumannii*. It has been reported that prophylactic or therapeutic use of antibiotics is an important risk factor for multidrug-resistant *Acinetobacter baumannii* infections. In our study, a meaningful statistical relation between carbapenem usage and PDR *Acinetobacter baumannii* infection was determined ( $p=0.001$ ). In a recent study examining resistance in *Acinetobacter baumannii*, Kim et al. [17] found out that cephalosporin and carbapenem usage constitute a risk factor in carbapenem-resistant *Acinetobacter baumannii* infections. In a study carried out by Aydemir et al. [18], who searched for risk factors affecting the mortality of resistant *Acinetobacter baumannii* infections, the use of carbapenem was detected to be a risk factor. Similarly, in our study, use of carbapenem in patients with *Acinetobacter baumannii* infections is a significant risk factor in PDR *Acinetobacter baumannii* infections.

In this study, PDR Acinetobacter baumannii infections were found to be resistant to all antibiotics except colistin, tigecycline, and aminoglycosides. Colistin and tigecycline are the predominant antibiotics used in the treatment of PDR Acinetobacter baumannii infections; combination therapy is also suggested due to serious mortality and morbidity associated with these infections. In an in-vitro study, carbapenem/sulbactam, colistin/rifampicin, and tigecycline/rifampicin combinations demonstrated increased efficiency [19,20]. Moreover, in clinical studies, cases were observed to be successfully treated with a combination of colistin and one or more of the following: carbapenem, aminoglycoside, and quinolon, or with the joint combination of colistin, tigecycline, and carbapenem [21,22]. In an in-vitro study performed in recent years, it was shown that a combination of colistin and teicoplanin was effective provided a serious synergy and was suggested as an option for treatment [23].

To prevent PDR Acinetobacter baumannii infections, effective infection control measures should also be taken. The determination of infection control measures and each hospital's strict implementation of its own measures may prevent Acinetobacter baumannii infections and increased resistance. In outbreaks caused by Acinetobacter baumannii, severe infection control measures including increased hand hygiene and environmental cleaning were found to contribute to the eradication of outbreak [2,4,24,25].

There were limitations in this study. First, this was a retrospective study conducted at a single medical center. Second, this study was resulted in incomplete data, and did not control for laboratory and clinical examinations of all patients.

In conclusion, PDR Acinetobacter baumannii infections are important nosocomial infections with a high mortality rate. Patients' carbapenem usage, their length of hospital stay, their history of stay in an internal intensive care unit, renal comorbid diseases, and a diagnosis of nosocomial pneumonia are important risk factors for PDR Acinetobacter baumannii infections.

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