

Original Article

Use of carbapenems and glycopeptides is significant risk for multidrug resistant *Acinetobacter baumannii* infections

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Abstract

Introduction: Multi-drug resistant *Acinetobacter baumannii* (MDR-Ab) infections are an important healthcare problem globally. The aim of this study was to evaluate risk factors associated with MDR-Ab infections in hospitalized patients in Turkey.

Methodology: A case-control study was performed in a tertiary care 1,303-bed university hospital, among case patients with MDR-Ab infections. The hospital records of case and control patients were retrospectively evaluated over a year. Patients who were hospitalized in the same department and in the same time interval as the case patients, without MDR-Ab infection or colonization, were chosen for control group. Demographic characteristics, Acute Physiology And Chronic Health Evaluation II (APACHE II) scores, comorbid diseases, use of invasive tools and duration of usage, and duration of use of antibiotics were recorded for all patients. Comparisons between case and control groups for possible risk factors were performed.

Results: In total, 95 cases and 95 controls were included in the study. Univariate analysis highlighted several variables as risk factors for MDR-Ab infections. Multivariate analysis showed that only antibiotic usage over seven days (OR = 2.38, CI = 1.18-4.83, p = 0.016) was found to be a significant risk factor. When antibiotic treatment patterns in both groups were compared, the use of carbapenems (p = 0.001) and glycopeptide antibiotics (p=0.001) in patient treatment were found significantly higher in the MDR-Ab case group.

Conclusion: This study showed us that previous antibiotic use is a significant risk factor for MDR-Ab infections. The use of carbapenems and glycopeptides should be considered as primary risk factors for developing MDR-Ab infection.

Key words: Acinetobacter; antibiotic; multi-drug resistance; infection; risk factors.

J Infect Dev Ctries 2018; 12(2):67-72. doi:10.3855/jidc.8081

(Received 03 January 2016 – Accepted 30 April 2016)

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Introduction

Acinetobacter baumannii emerged as nosocomial infectious agents during the last two decades in many hospitals all around the world. This Gram-negative coccobacillus is ubiquitous and occurs mostly as commensals on the skin and in the environment [1-3]. Niche adaptation of *Acinetobacter* species to survive in hospital environments had enabled *Acinetobacter* strains to develop resistance against the first line antimicrobials [4,5].

In the last decade, multidrug resistant (MDR) strains were reported from Turkish hospitals which has become more common in recent years [6]. MDR *Acinetobacter baumannii* (MDR-Ab) strains can complicate the treatment regime of serious infections especially since these strains have begun to develop resistance to the carbapenems [7-9]. Clinical forms of infections due to *Acinetobacter* vary and include

pneumonia, particularly ventilator-associated pneumonia (VAP) in intensive care units (ICUs). *Acinetobacter* species can also be isolated from bloodstream infections (BSI), surgical site infections (SSI), urinary care units (ICU tract infections (UTI), body fluids from sterile body sites, and bone and soft tissue infections. [10]. Risk factors of *Acinetobacter* infections are important in order to prevent and control related infections.

MDR-Ab was associated with the use of broad spectrum antibiotics in hospitals and previous use of antibiotics have been reported as an independent predictor for infection and/or colonization of MDR-Ab [11]. The frequency of MDR-Ab strains reported in studies varies depending on the type and treatment regime of antibiotics administered. Previous studies have shown an association with the use of third

generation cephalosporins, fluoroquinolones, and carbapenems [12-14].

The risk factors of developing MDR *Acinetobacter* infections in Turkish hospitals require additional studies. Analysing risk factors of retrospective *Acinetobacter* infections would be helpful to understand and prepare prevention strategy in hospital settings in the future [15]. The aim of this study was to investigate risk factors of developing MDR-Ab infections in a large university hospital using a well-designed case control study. In addition, this study examined the efficacy of antibiotic treatment on the MDR-Ab infections.

Methodology

Study Setting

This study was performed in Dicle University Hospital (DUH) between April 2011 and April 2012. DUH is a referral healthcare centre and the largest hospital complex in southeast of Turkey with 1303-bed capacity which services approximately four million people. The hospital complex consists of a Main Building, Children's Hospital and Oncology Centre. Patients from clinics and intensive care units were included into the study.

Study Design

Hospital surveillance data were evaluated during the study period retrospectively. Related data of the patients were obtained from medical files and obtained from the hospital surveillance program.. This case-control study defined the case group as hospitalized patients with symptomatic nosocomial MDR-Ab infections that had been developed during the study period. The diagnoses of nosocomial infections were

made using the 'Center for Disease Control and Prevention' (CDC) criteria [16,17].

The patients were followed up by ward doctors and infectious diseases specialists. All cases were evaluated and recorded by Infection Control Program workers for nosocomial infection control program. Asymptomatic MDR-Ab culture positive patients was defined as being "colonized" and these patients were not included in the study or control groups. MDR-Ab was defined if the *Acinetobacter* strain was resistant to a carbapenem along with being resistant to three or more of the following antibiotics: amikacin, ceftazidime, cefepime/sulbactam, ciprofloxacin, piperacillin/tazobactam, and tetracycline. The data was transferred into a specific data collection database which included multiple hospital associated risk factors in addition to demographic aspects (see statistical methodology). The date of the first positive culture of MDR-Ab infection was recorded for each case. This data was used for calculation of hospitalization period. Repeated isolations of MDR-Ab were not considered.

The control group was matched with cases and was defined as a patient who was hospitalized as the next case in the same department with a case patient, without MDR-Ab infection or colonization. The study design included one control patient for each case patient (1:1). The patients were followed up to discharge from hospital and outcomes were recorded.

For both groups' demographic characteristics, reason for hospitalization, APACHE II score, comorbid diseases, previous hospitalization story, duration of hospitalization, invasive device use, duration of antibiotics used, and outcome were recorded (Table 1). For statistical analysis, only the data before culturing time were used for the MDR-Ab group.

Table 1. Univariate analysis of risk factors associated with developing MDR-Ab infections in case and control groups.

Variables	Cases, n (%)	Controls, n (%)	p
Urinary catheter (>7 days)	57 (60)	36 (37,9)	0,002
Endotracheal intubation (>3 days)	34 (35,8)	16 (16,8)	0,002
Mechanical ventilation	59 (62,1)	43 (45,3)	0,014
CVC (>7 days)	40 (42,1)	19 (20)	0,001
H ₂ RB use (>7 days)	67 (70,5)	42 (44,2)	<0,001
TPN	48 (50,5)	31 (32,6)	0,009
Enteral feeding	52 (54,7)	35 (36,8)	0,010
Surgical drainage	12 (12,6)	7 (7,4)	0,167
Tracheostomy	9 (9,5)	4 (4,2)	0,125
Hemodialysis	5 (5,3)	2 (2,1)	0,222
Surgery	38 (40)	35 (36,8)	0,383
Bronchoscopy	0 (0)	1 (1,1)	0,500
Immunosuppressive therapy	3 (3,2)	1 (1,1)	0,310
Foreign body, prosthesis	6 (6,3)	0 (0)	0,014
Nasogastric tube (>7 days)	30 (31,6)	14 (14,7)	0,005
Antibiotic use (>7 days)	75 (78,9)	53 (55,8)	0,001
APACHE II (SD)	17,6 (± 8,1)	15,2 (± 7,4)	0,038

Laboratory

The culturing of study samples were undertaken at the Department of Infectious Diseases Laboratory and Central Laboratory of Dicle University Hospital. Samples including blood, urine, bronchoalveolar lavages, deep tracheal aspirates, sputums, throat swaps, wound/tissue samples, cerebrospinal fluids (CSF), catheter tips, drainage samples, pleural fluids, ascites fluids, abscess materials and stool were cultured. Blood specimens were collected from both arms of the patients, inoculated into the blood culture vials (BACTEC) and processed via BACTEC 9240 and BACTEC 9120 Becton Dickinson blood culture systems (Sparks, Maryland, USA). Specimens were cultured when the blood culture vial signalled as positive. Urine and other clinical specimens were collected using appropriate sample collection tubes. The samples were cultured on Eosine Metilen Blue and Blood agar plates (Oxoid, Hampshire, UK). The plates were incubated in a 37 °C incubator. If bacterial growth was observed on the plate, presumptive *Acinebacter* isolates, which were Gram-negative diplococci, oxidase-negative and non-lactose fermenting, were identified using Phoenix 100 (Becton Dickinson, Sparks, Maryland, USA) identification system. Antimicrobial susceptibility of *Acinetobacter baumannii* was confirmed using disc diffusion test (Oxoid, Hampshire, UK).

Statistical Analyses

All data was entered into Microsoft Excel program and the data was analyzed using SPSS version 20.0 (SPSS Inc, Chicago, USA). Comparisons between groups for possible risk factors were performed using Chi square and Student's t test. The continued variables were recorded as numbers. Dichotomy variables such as gender were recorded as 0 and 1. Time related risk factors such as invasive interventions and drug use were converted into dichotomy variables using a cut off value (urinary catheter use (> 7 days), central venous catheter use (> 7 days), nasogastric tube use (> 7 days), H₂ Receptors blockers use (>7 days), endotracheal intubation (> 3 days), mechanical ventilation (> 3 days), total antibiotic use (> 7 days). In the univariate analyse, binary variables were compared using Chi square test, continued variables were compared using Student's t test. p value was accepted significant if < 0.05. MDR-Ab risk factors were evaluated in multivariate analyses approach using regression analyse. The significant variables in univariate analyses were transferred into a logistic regression model. The variables were entered into Logistic Regression Model if they were significant

in the univariate analyses. The variables were accepted as risk factors if these are significant in the Logistic Regression analyse.

The study was approved by Dicle University Hospitals Ethical Committee. (Approve No: 117-22.04.2011).

Results

During the study period, 95 case patients and 95 control patients were included. The mean age of the case group was 38.1 ± 25.7 years; mean age of the control group was 43.9 ± 26.9 years ($p=0,131$). The gender distribution was similar with 48 (50.5%) patients in the case group and 46 (48.4%) patients in the control group being male ($p = 0,442$).

The case patients with MDR-Ab infections were followed up and most frequently located in Anaesthesiology ICU (21 cases, 22.1%), Pulmonary Diseases ICU (18 cases, 18.9%) and Burn Unit (14 cases, 14.7%). Primary diagnoses of the patients in the both groups were similar. The most common diagnoses at the admission were multiple trauma, burns and pneumonia. The majority of MDR-Ab cases were diagnosed in ICUs (82 cases (86.3%) in ICUs vs. 13 cases (13.7%) in other departments). The sources of MDR-Ab isolates were blood samples found in 28 (29.5%) cases, deep tracheal fluids found in 28 (29.5%) cases, tissue/wound samples found in 25 (26.3%) cases, urine in four (4.2%) cases, central venous catheter' tips in four (4.2%) cases and others clinical specimens in six (6.3%) cases.

The severity indexes of patients were different between the case and the control groups. The mean of APACHE II scores of the patients in the case group was $17.6 (\pm 8.1)$ whereas in the control group the score was $15.2 (\pm 7.4)$ ($p = 0.038$). Duration from hospitalization to culturing time was 16.6 ± 21.9 days within the case group and 10.7 ± 11.3 days in the control group ($p=0.022$).

The numbers of comorbidities of the patients were found similar in both case and control groups except cerebrovascular diseases. Cerebrovascular diseases were found significantly higher among the case group (13 patients, 13.7%) vs. the control group (4 patients, 4.2%), $p = 0.020$.

Significant risks factors found in the univariate analysis for developing MDR-Ab infection included: duration of hospitalization, total parenteral nutrition, feeding with enteral tube, cerebrovascular disease, urinary catheter indwelling (> 7 days), endotracheal intubation (> 3 days), mechanical ventilation, APACHE II scores, central venous catheter

implementation (> 7 days), nasogastric tube indwelling (> 7 days), H2 receptors blocker use (>7 days) and antibiotic use longer than seven days (> 7 days) (Table 1).

Logistic regression model analysis showed antibiotic use longer than seven days (OR = 2.61, CI = 1.26-5.40, $p = 0.010$) to be the only significant risk factors for developing MDR-Ab infection. The other factors were not significant for MDR-Ab infection (data not shown).

Comparison analysis of antibiotic treatment of patients between cases and controls found the use of carbapenems and glycopeptides to be significantly higher in the MDR-Ab case group. In the comparison analysis of antibiotic groups, only univariate analysis was used (Table 2). During hospitalization, 54 patients (56.8%) in MDR-Ab case group vs. 31 patients (32.6%) in non-MDR-Ab control group were treated with carbapenems (imipenem cilastatin and meropenem) ($p = 0.001$). Similarly, 31 patients (32.6%) in the case group and 10 patients (10.5%) in the control group were treated with glycopeptides ($p=0.001$). There was no significant difference between two case and control groups with other antimicrobials treatment (Table 2). Comparison analysis regarding the duration of antimicrobial treatment for case versus control groups respectively found that treatment was significantly longer in the MDR-Ab case group: durations of carbapenems treatment (6.7 ± 9.0 days vs. 2.9 ± 5.7 days, $p = 0.001$), glycopeptides treatment (3.2 ± 6.2 days vs. 1.2 ± 4.2 days, $p = 0.009$) and linezolid treatment (1.5 ± 4.8 days vs. 0.4 ± 2.0 days, $p = 0.039$).

The mortality rates were different in two groups. Thirty-seven patients died (38.9%) in the case group and 23 patients died (24.2%) ($p = 0,021$) in the control group. The attribution of MDR-Ab was not investigated.

Discussion

During last two decades, MDR *Acinetobacter baumannii* infections have become a serious problem in intensive care units, across multiple countries, exacerbated by the lack of infection control measures, particularly in developing countries. In this study, the potential risk factors associated with developing MDR-Ab infections among hospitalized adult patients were evaluated in a large university hospital in Turkey. In our study several potential risk factors were evaluated and several factors were found significant in univariate analysis. In ICUs, invasive procedures such as mechanical ventilation implementation, CVP catheter use and urinary catheter use are the most important invasive treatment modalities. Especially prolonged invasive procedures should be managed carefully. Previous studies showed extensive role of mechanical ventilation among different patient groups for multidrug resistant microorganisms' transmissions and infections. A study from Thailand reported that mechanical ventilation prolonged longer than one week was one of the risk factors of MDR *A. baumannii* infections [18]. In this study, in the multivariate analysis, only antibiotic usage over seven days was found as significant a factor for MDR *Acinetobacter baumannii* infections.

This study then used a multivariate analysis and found that antibiotic use the sole significant risk factor. Further analysis indicated that consumption of some antimicrobials could be risk factors, in particular the use of carbapenems and glycopeptides (Table 2). In addition, the length of course including three antimicrobials (carbapenems, glycopeptides and linezolid) use was found significant for developing MDR-Ab infection. This study's findings are comparable with previous studies where use of beta-lactam/beta-lactamase inhibitor antibiotics and use of carbapenem antibiotics were reported as significant risk

Table 2. Univariate analysis of antibiotic treatment associated with developing MDR-Ab infections in case and control groups.

Antibiotic Groups	Case Group, n (%)	Control grub, n (%)	p
1. G Cephalosporins	11 (11,6)	19 (20)	0,081
3. G Cephalosporins	38 (40)	39 (41,1)	0,500
Aminoglycosides	16 (16,8)	9 (9,5)	0,099
Ampicillin/Sulbactam	5 (5,3)	6 (6,3)	0,500
Piperacillin/Tazobactam	18 (18,9)	13 (13,7)	0,216
Sefoperazon/Sulbactam	10 (10,5)	6 (6,3)	0,217
Carbapenems	54 (56,8)	31 (32,6)	0,001
Glycopeptides	31 (32,6)	10 (10,5)	0,001
Tigecycline	0 (0)	1 (1,1)	0,500
Quinolones	0 (0)	3 (3,2)	0,123
Linezolid	11 (11,6)	5 (5,3)	0,095
Antifungals	3 (3,2)	1 (1,1)	0,310

factors associated with MDR *A. baumannii* bacteraemia in Thailand [18] and where receiving surgery, tracheal intubation and mechanical ventilation for more than 10 days and previous use of carbapenems were reported as independent risk factors for developing carbapenem resistant *A. baumannii* infections in China [19].

It is well known that bacteria are naturally resistant to many antibiotics and are able to acquire additional resistance mechanisms. It is therefore expected that previous use and exposure of broad-spectrum antibiotics could contribute to the development of MDR-Ab strains circulating in hospitals. Several broad spectrum antimicrobial classes studies have contributed to the development of MDR-Ab infections which include prior use of antimicrobials, especially carbapenems [12,20-22], third-generation cephalosporins [23-25], and/or fluoroquinolones [26] as independent risk factors. These studies reported various levels of significance for the use of difference antimicrobial classes in association with developing MDR-Ab infections. In 2006, Falagas and Kopterides, in a systematic review of the literature, pointed out important features and weaknesses of the studies which investigated developing MDR-Ab infection risk factors. They reported that in majority of these studies; “use of carbapenems and third-generation cephalosporins appear to be related to the development of an MDR phenotype by *A. baumannii*”. The designs of these studies were heterogeneous and investigation of risk factors was limited. The acquisition and spread of MDR *A. baumannii* could be related to a large number of variables. They drew attention to a problematic area that odds of antibiotic groups use for the MDR-Ab acquisition was closely related with features of control groups in these studies [27].

Globally, the frequency of MDR *Acinetobacter* reports have increased steadily over the years and the antimicrobial resistance in the hospitals have become an increasing problem in the last two decades and Turkey has seen this issue in particular with *Acinetobacter* infections in ICUs. According to official reports of Turkish Ministry of Health, the number of ICU beds has remarkable increased in Turkey between 2001 and 2012 [28]. Therefore, infection control precautions and prevention of MDR microorganisms’ transmission in ICUs are more crucial in order to prevent infections. In an ICU setting, the prevention of developing MDR-Ab infections requires additional controls such as high level hand hygiene adherence and implementation of antimicrobial stewardship programs.

This study has some limitations. One of these limitations was the significant difference between

APACHE II scores of the case group and control group. The cases were severe than the controls and the treatment duration of carbapenems, glycopeptides and linezolid were found longer. Meanwhile APACHE II score was not found significant in the multivariate analyses. The other limitation is about the variety of the patients’ diagnoses. At the admission, the diagnoses of our patients were assorted. Beside this situation, the primary diagnoses of the patients in the both groups were found similar.

Conclusions

The development of MDR-Ab infections in hospitalized patients continue to be a major health problem in Turkey. This study showed that previous antibiotic use is the significant risk factor for developing MDR-Ab infections. Use of carbapenems and glycopeptides should be considered as primary risk factors for developing MDR-Ab infections.

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Conflict of interests: No conflict of interests is declared.