ORIGINAL ARTICLE

Cemal Ustun[1]
Salih Hosoglu [2]
Mehmet Faruk Geyik[3]

[1]Abant Izzet Baysal University, Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, Bolu, Turkey
[2]Fatih University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[3]Düzce University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, Düzce, Turkey

Corresponding Author:
Dr. Salih Hosoglu, Fatih University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
Email: hosoglu@hotmail.com

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konuralptipdergi@duzce.edu.tr
konuralpgeneltip@gmail.com
www.konuralptipdergi.duzce.edu.tr

Risk Factors for Multi-Drug-Resistant *Pseudomonas aeruginosa* Infections in a University Hospital-A Case Control Study

ABSTRACT
Purpose: This study aims to determine the risk factors associated with multi-drug-resistant *Pseudomonas aeruginosa* (MDR-Pa) infections.
Methods: A case control study was conducted at the Dicle University Hospital which is 1150-bed tertiary care teaching hospital in Diyarbakir, Turkey. The study cases were recruited from patients with nosocomial MDR-Pa infections. Two control cases were arranged to compare risk factors of MDR-Pa infections. One of the control groups was composed of patients with non-MDR-Pa infections and the other group with non-MDR Gram-negative bacterial infections except *P. aeruginosa*.
Results: Overall, 225 patients were included in the study, 75 with MDR-Pa infections, 150 control cases (75 non-MDR-Pa and 75 MDR Gram-negative non *P. aeruginosa* infections). The incidence of MDR-Pa infections was found as 3.1/1,000 admissions. Multivariate analysis showed that multiple invasive procedures (Relative Risk 24.57 (95% Confidence Interval 4.45-135.73) p<0.001), burn (RR 13.66 (CI 407-45.80) p<0.001), malignity (RR 12.50 (CI 2.64-59.20) p=0.001), pneumonia (RR 11.91 (CI 2.44-58.16) p=0.002), carbapenem use (RR 4.92 (CI 1.60-15.09) p=0.005) and long hospitalization (> 10 days) (RR 4.68 (CI=2.09-10.49) p<0.001), were found to be risk factors for MDR-Pa.
Conclusions: This study revealed that severity of clinical course and carbapenem use are significant risk factors for MDR-Pa infections.
Keywords*: Pseudomonas aeruginosa*, Multi-Drug Resistance, Risk Factors

Bir Üniversite Hastanesinde Çoklu Antibiyotik Dirençli *Pseudomonas aeruginosa* Enfeksiyonları İçin Risk Faktörleri-Bir Vaka-Kontrol Çalışması

ÖZ
Amaç: Bu çalışma, çoklu ilaca dirençli *Pseudomonas aeruginosa* (MDR-Pa) enfeksiyonları ile ilişkili risk faktörlerini belirlemeyi amaçlamaktadır.
Gereç Ve Yöntem: Bu çalışma bir vaka kontrol çalışması olarak 1150 yataklı üçüncü basamak eğitim hastanesi olan Dicle Üniversitesi Hastanesi'nde (Diyarbakır, Türkiye) yapıldı. Vakalar nozokomiyal MDR-Pa enfeksiyonu olan hastalardan oluşturuldu. MDR-Pa enfeksiyonlarının risk faktörlerini araştırmak için her bir vakaya karşılık iki kontrol hastası alındı. Kontrol gruplarından birisi MDR olmayan *P. aeruginosa* (non-MDR-Pa) enfeksiyon hastaları, diğerini *P. aeruginosa* hariç olmak üzere MDR olmayan gram negatif bakteriyel enfeksiyon hastaları oluşturdu.
Bulgular: Toplamda 225 hastadan oluşan çalışmaya 75 MDR-Pa enfeksiyonu olan hasta, 150 de kontrol hastası (75 non-MDR-Pa ve 75 non-MDR *P. aeruginosa* dışı Gram-negatif enfeksiyonları) dahil edildi. MDR-Pa enfeksiyonlarının insidansı 3.1/1000 kabul olarak bulunmuştur. Çok değişkenli analiz sonuçlarına göre birden fazla invaziv girişim (Göreli Risk 24.57 (% 95 Güven Aralığı 4,45-135,73) p <0.001), (RR 13.66 (CI 407-45,80) p <0.001), malignite (RR 12.50 (CI 2,64-59,20) p = 0.001), pnömoni (RR 11.91 (CI 2,44-58,16) p=0.002), karbapenem kullanımı (RR 4.92 (CI 1,60-15,09) p = 0.005) ve uzun süre yatış (> 10 gün) (RR 4.68 (CI = 2.09 - 10,49) p <0.001), MDR-Pa için risk faktörleri olarak bulundu.
Sonuç: Bu çalışma, klinik seyir şiddeti ve karbapenem kullanımının MDR-Pa enfeksiyonları için önemli risk faktörleri olduğunu ortaya koymuştur.
Anahtar Kelimeler: *Pseudomonas aeruginosa*, Çoklu İlaç Direnci, Risk Faktörleri

INTRODUCTION

Pseudomonas aeruginosa is one of the most frequent nosocomial pathogens, usually responsible for life-threatening nosocomial infections including ventilator-associated pneumonia, burn and surgical site infections (1-4). It is naturally resistant to many antimicrobials, with a high-level resistance mechanism acquired under selective pressures resulting from antimicrobial drug usage (1,2,4-8).

In recent years, nosocomial multi-drug-resistant *Pseudomonas aeruginosa* (MDR-Pa) infections have become a growing healthcare problem worldwide. Recently, the prevalence of these infections has increased in rates of morbidity, mortality, and cost (1,2). Also, alternative treatment choices are almost exhausted; the clinicians are thus confronting serious problems in the clinical management of these infections (3,6,8). Nosocomial MDR-Pa may spread patient-to-patient and result in severe adverse outcomes (1,2,9,10).

Some studies reported possible risk factors for MDR-Pa infections such as broad-spectrum antimicrobial usage, undergoing surgery, severity of illness, previous hospitalization, long-term hospitalization, intensive care unit (ICU) stay, patient-nurse rate, effectiveness of infection control measures and immunosuppression (4-7,9,11,12). Recently, nosocomial MDR-Pa infections constituted an important problem in many hospitals including our hospital; and the prevalence of these infections increased. It is import to understand the possible risk factors to prevent these infections. The aim of this study was to identify the risk factors for nosocomial MDR-Pa infections.

MATERIALS AND METHODS

Hospital setting

This case-control study was conducted at Dicle University Hospital (DUH), an 1150-beds university hospital, between January-August 2007. DUH is the largest hospital in Diyarbakir city center, southeast Turkey, containing all major medical and surgical departments as well as adult and pediatric ICUs with total of 80 beds. Approximately 40,000 patients were hospitalized annually in the DUH in the last five years, and about 1,600 of these were treated in the ICUs. A moderately effective restricted antibiotic policy has been implemented in the hospital since 2003. Within this program, only Infectious Disease specialists prescribe imipenem, meropenem, amikacin, third generation cephalosporins, cefepime, piperacillin/tazobactam, parenteral fluoroquinolones, vancomycin, teicoplanin, linezolid, and antifungal agents.

Study Design

A case-control study was performed by the study team. The team included an Infectious Disease specialist, a resident physician and two infection control nurses. Nosocomial infections were diagnosed according to criteria established by the Centers for Disease Control and Prevention.[13] All cases with MDR-Pa infection were included in the study group during the study period. The control patients were selected from among the patients with nosocomial infections during routine surveillance. The next eligible patient was included in the study as control. Two appropriate control patients were allocated to each study case.

A list of the possible risk factors was drawn from previous studies and our clinical experiences. This list was used to produce a standard form including the patients' demographic features, laboratory values, APACHE II score, co-morbidities (malignancy, immunosuppression, cardiovascular diseases, chronic renal or hepatic failure, hemodialysis, diabetes mellitus, chronic lung diseases, malnutrition, transplantation), invasive procedures (mechanical ventilator, central venous catheter, nasogastric tube, tracheostomy catheter, thoracotomy catheter, gastrostomy catheter, external cerebrospinal fluid drainage catheter, urinary catheter, multiple peripheral venous catheter, surgical drainage catheter), length of hospitalization, length of ICU stay, surgical intervention, total parenteral nutrition (TPN), use of H_2 receptor blockers, antimicrobial susceptibility test results, hospitalization in the last six months, undergoing intensive care, prophylactic antibiotic usage, use of antimicrobials and use of immunosuppressive agents. In addition, patient outcomes were recorded until discharging from hospital or death. The form was filled for each study and control patient.

Definitions

Patients with MDR-Pa infections were defined as study cases. The control group included patients with nosocomial infections which were either non-MDR-Pa or non-MDR, Gram-negative bacterial infection except *P. aeruginosa*. The term MDR was used when the organism was resistant to imipenem and meropenem in addition to three or more of the following antibiotics: ceftazidime, cephepime, aztreonam, amikacin, piperacillin, and ciprofloxacin. Susceptibility to imipenem and meropenem in addition to four or more of ceftazidime, cephepime, aztreonam, amikacin, piperacillin, and ciprofloxacin was defined as non-MDR. Hospitalization of 14-days or longer was defined as "long term hospitalization". A “multiple invasive procedures" was assigned if a patient had undergone two or more of the following invasive procedures: mechanical ventilator, central venous catheter, and urinary catheter.

Data Collection

All patients were visited by an Infectious Disease specialist and a resident physician experienced in the field of nosocomial infections. Microbiologic data were collected from the

following clinical specimens: blood, urine, sputum, tracheal aspirate, wound, catheter tips, peritoneal fluid, pleural fluid, and cerebrospinal fluid. Microorganisms were identified at the Infectious Disease and Clinical Microbiology Laboratory. The patients' data were obtained from medical charts and laboratory database and recorded on the standard forms.

All study cases and controls were followed until discharge from hospital or death, if the latter occurred during hospitalization. The BD Phoenix System was used for identification and determination of susceptibility to antimicrobials. In addition, conventional methods were used to identify *P. aeruginosa*, such as Gram stain, cytochrome oxidase reaction, pigment production, detection of aromatic smell, and macroscopic appearance of colonies. Imipenem and meropenem resistance was confirmed by the Disc Diffusion test (Oxoid). Intermediate-susceptible strains and colonization process were not included in the study.

Statistical Analysis

SPSS 16.0 version for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses. Probable risk factors for nosocomial MDR-Pa cases and controls were compared by using the *Chi-square* test for binary variables and *Student's t*-test for continuous variables.

Variables with a *p*-value <0.1 in the univariate analysis were included in the logistic regression model for multivariate analysis. The conditional backward stepwise method was used in the multivariate logistic regression model; variables attributed a *p*-value <0.05 were accepted as significant for developing nosocomial MDR-Pa infection.

RESULTS

A total of 225 patients with nosocomial infections were included in the study. Of these, 75 were cases and 150 were controls. The incidence of MDR-Pa infections was found to be 3.1 per 1,000 admissions. The mean age of cases was 29.8 years (± 27.2) and controls 37.9 years (± 26.8). The gender distribution of cases and controls was similar. The other selected characteristics of cases and controls were found different (Table 1). MDR-Pa causative agents were frequently isolated from the Burn Unit (28%), Reanimation ICU (13%), Plastic Surgery Department (13%) and Pediatric ICU (13%).

Univariate analyses revealed multiple risk factors for MDR-Pa infections. Gender was not a risk factor for MDR-Pa infections but APACHE II score >10 was found significant (Table 2). Carbapenems (39%) and first generation cephalosporins (39%) were the most commonly used antibiotics in the last six-month period for MDR-Pa cases. A total of 18 variables were found significant for MDR-Pa infections (Table 2).

In the multivariate analysis, multiple invasive procedures (Relative Risk 24.57 (Confidence Interval 4.45-135.73) p<0.001), burn (RR 13.66 (CI 407-45.80) p<0.001), malignity (RR 12.50 (CI 2.64-59.20) p=0.001), pneumonia (RR 11.91 (CI 2.44-58.16) p=0.002), carbapenem use (RR 4.92 (CI 1.60-15.09) p=0.005) and long hospitalization (>10 days) (RR 4.68 (CI 2.09-10.49) p<0.001) were found to be risk factors for MDR-Pa. Bacteremia/sepsis (RR 4.67 (CI 0.93-23.48) p=0.61) and Diabetes Mellitus (RR 5.21 (CI 0.98-27.71) p=0.53) were found non-significant.

Table 1. The characteristics of MDR-Pa cases and control groups.

Variables	MDR-Pa **(n=75)**	**Control (n=150)**	**p**
Male gender (%)	44 (58.7)	98 (65.3)	0.329
Age (yrs, mean ± SD)	29.8 ±27.2	37.9±26.8	0.035
Mortality rate (%)	19(25.3)	13 (8.7)	0.070
Length of hospitalization (days, mean ± SD)	90±115	35±52	0.001

Table 2. Variables tested for risk factors of MDR-Pa infections by univariate analysis

Variables	MDR-Pa *n*(%)*	Control *n (%)*	OR (95% CI)	*p*
Gender (male)	44 (58.7)	98 (65.3)	0.89 (0.72-1.12)	0.380
Age	29.8 ± 27.2	37.9 ± 26.8		0.035
APACHE II score >10	29 (38.7)	22 (14.7)	2.63 (1.63-1.26)	<0.001
Prior hospitalization	33 (44.0)	74 (48.0)	0.89 (0.66-1.21)	0.481
Hospitalization longer than 10 days	56 (74.7)	57 (38.0)	1.97 (1.54-2.51)	0.03
ICU stay in the last six months	13 (17.3)	29 (19.3)	0.90 (0.50-1.62)	0.717
Multiple pathogens	27 (36.0)	18 (12.0)	3.00 (1.77-5.09)	<0.001
Multiple invasive procedures	31 (41.3)	19 (12.7)	3.26 (1.98-5.38)	<0.001
Mechanical ventilator	30 (40.0)	18 (12.0)	3.33 (1.99-5.58)	<0.001
Central venous catheter	21 (28.0)	24 (16.0)	1.75 (1.05-2.93)	0.034
Foley catheter	41 (54.7)	60 (40.0)	1.37 (1.03-1.82)	0.037
Total parenteral nutrition	12 (16.0)	28 (18.7)	0.86 (0.46-1.59)	0.622
Blood transfusion	51 (68.0)	78 (52.0)	1.31 (1.05-1.63)	0.046
Surgical intervention	20 (26.7)	66 (44.0)	0.61 (0.40-0.92)	0.012
Prophylactic antibiotic use	47 (62.7)	91 (60.7)	1.03 (0.83-1.28)	0.772
H_2 blocker use	58 (77.3)	69 (46.0)	1.68 (1.36-2.08)	<0.001
Pneumonia	14 (18.7)	5 (3.3)	5.6 (2.10-14.96)	<0.001
Bacteremia/sepsis	11 (14.7)	4 (2.7)	5.5 (1.81-16.69)	0.01
Burn	34 (45.3)	31 (20.7)	2.19 (1.47-3.27)	<0.001
Neurological disease	9 (12.0)	22 (14.7)	0.82 (0.40-1.69)	0.584
COPD*	9 (12.0)	14 (9.3)	1.27 (0.58-2.83)	0.534
Chronic renal failure	3 (4.0)	10 (6.7)	0.60 (0.17-2.12)	0.42
Diabetes mellitus	7 (9.3)	14 (9.3)	1.0 (0.42-2.37)	1.00
Immunosuppressive drug use	7 (9.3)	12 (8.0)	1.17 (0.48-2.84)	0.735
Hemodialysis	5 (6.7)	1 (0.7)	10.00 (1.19-84.07)	0.08
Malignancy	12 (16.0)	13 (0.87)	1.85 (0.87-3.85)	0.099
Antibiotic use				
Carbapenem	29 (38.7)	9 (6.0)	6.44 (3.22-12.91)	<0.001
First generation cephalosporins	29 (38.7)	44 (29.3)	1.32 (0.90-1.92)	0.159
Third generation cephalosporins	16 (21.3)	40 (26.7)	0.80 (0.48-1.33)	0.383
Amikacin	11 (14.7)	7 (4.7)	3.14 (1.27-7.78)	0.009
Piperacillin/tazobactam	5 (6.7)	1 (0.7)	10.00 (1.19-84.07)	0.008
Ampicillin/sulbactam	14 (18.7)	14 (9.3)	2.00 (1.00-3.98)	0.46
Ciprofloxacin	10 (13.3)	30 (20.0)	0.67 (0.35-1.29)	0.218
Glycopeptide	6 (8.0)	12 (8.0)	1.00 (0.39-2.56)	1.000

* Chronic Obstructive Pulmonary Diseases

DISCUSSION

In this study; multiple invasive procedures, severe clinical entities such as malignity and pneumonia, carbapenem use and long hospital stay were found as significant associated factors for MDR-Pa infections. At the same time, the incidences of MDR-Pa have been found as 3.1/1,000 admissions which to vary between 0.14/1,000 and 1.4/1,000 admissions in previous studies (7,9,14). This remarkable high rate of *P. aeruginosa* indicates that our hospital has a serious MDR-Pa issue.

Prior to the use of antimicrobials, especially use of carbapenem and fluoroquinolones was reported as a major risk factor for MDR-Pa infection in the meta-analysis by Falagas (4). Similar results have also been reported in some previous studies (5,7,9) According to the previous reports, the emergence and spread of MDR PA could be related to the previous and/or over-use of antimicrobials. In many of the previous studies, an association between use of carbapenems and resistance of *P. aeruginosa* has been reported (5,7,9,11,15-18). However, a study from India showed close correlation between antimicrobial use and MDR-Pa but not any correlation between carbapenem use and resistance in P. aeruginosa. Their study identified that meropenem use is an independent risk factor for MDR-Pa (19). Our

results showed a strong association between carbapenem use and MDR-Pa infection, in univariate and in multivariate analysis. All of these consequences confirm a significant association between antimicrobial use and MDR-Pa infection, even though the correlation was not reported in some studies. Therefore, antimicrobial usage, especially carbapenem use should be controlled and minimized by clinicians in the hospital setting.

In this study, MDR-Pa was the most frequently isolated causative agent in the burn unit, plastic surgery, and ICUs. Defez have reported that MDR-Pa cases are more frequently hospitalized in surgical units and ICUs than in any other departments (7). Aloush reported that MDR-Pa cases were frequently diagnosed in chronic care facilities (9). Long time hospitalization in critical unites could be a risk factor for acquisition of MDR-Pa infections. Bacteremia/sepsis and diabetes mellitus were not significant factors in multivariate analyses. The courses of these diseases require long time hospitalizations with many invasive and non-invasive treatments along with heavy antimicrobial use. MDR-Pa was isolated most frequently from burn wounds, urine samples and respiratory tract specimens in previously reported studies (7,11,15). Therefore the patients in chronic care should be observed for the onset of MDR-Pa infection.

These results indicate that the invasive procedures and intensive antibiotic usage constitute a high risk for the acquisition of MDR-Pa infections. The use of mechanical ventilation, central venous catheter and urinary catheter had shown a correlation with MDR-Pa infections in several studies (4,5,7,9). Aloush have likewise reported a significant relationship between MDR-Pa infection and the multiple invasive different procedures score; their study and the present one have evaluated the role of multiple invasive procedures summarized by a high multiple invasive procedures score (9). Physicians should be aware of the risk of MDR-Pa infections among the patients who are required to have a number of invasive procedures.

This study has some limitations. Some of the characteristics of the control groups differed from those of the study cases. We could not supplement this case control study with a pulse-field gel electrophoresis (PFGE) typing of MDR-Pa isolates. The study identified chronic care patients, surgical intervention, total parenteral nutrition, sepsis and pneumonia as protective factors for MDR-Pa infection. We could not explain these results by our present knowledge. These factors should be tested in further studies to be performed in our geographic area.

In conclusion, this study has identified that patients with the following conditions should be carefully followed: long term hospitalization, multiple invasive procedures, co-morbidities and antimicrobial usage, especially carbapenems. The incidence of MDR-Pa should be followed carefully in hospital surveillance system.

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