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Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant acinetobacter baumannii

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SUMMARY

Background: A. baumannii is an important nosocomial pathogen associated with high mortality, morbidity and medical cost.
Aim: The aim of this study was to investigate risk factors for MDR *A. baumannii* bacteremia and also evaluate cost of hospitalization of these patients.
Methods: Study was conducted in Ankara Atatürk Training and Research Hospital. Patients who were hospitalized in ICU and diagnosed for nosocomial blood stream infection (BSI) between January 2007 and December 2010 were checked retrospectively. Patients with nosocomial BSI caused by multidrug resistant *A. baumannii* were compared with the patients who had BSI caused by other Gram-negative microorganisms in terms of risk factors, mortality and medical costs.
Findings: In multivariate analysis previous use of carbapenem, quinolone and metronidazole, and SAPS II score were found as independent risk factors. In case group; immunosupression, SAPS II score, and hospital stay until infection were independently associated with mortality in multivariate analysis.
Conclusion: Our results suggest that the occurrence of MDR *A.baumannii* bacteremia was related with the usage of the wide spectrum antibiotics, and mortality rates were increased in patients that high SAPS II scores, long term hospitalization. Infection control procedures and limited antibiotic usage are very important for prevent nosocomial infections.

1. Introduction

Hospital acquired infections are leading causes of morbidity and mortality due to increasing rate of antibiotic resistance. Especially, patients followed in the intensive care units (ICU) are under high risk of infections caused by resistant microorganisms.[1]

Rapid development and global spread of *A. baumannii* as a major cause of nosocomial infections is really remarkable. This organism tends to develop resistance against many antimicrobials from different groups.[2,3] In the 21st century, *A. baumannii* is frequently observed as a nosocomial infection which causes high mortality, morbidity and hospitalization cost.[4,5] Crude mortality rate and attributable mortality of the infection were reported to be 52% and 10-35%, respectively.[6]

The aim of this study was to explore the risk factors in patients with multi-drug resistant (MDR) *A. baumannii* bacteremia and perform a cost analysis of this clinical problem.

2. Material and Methods

This retrospective cohort study has included the patients who had nosocomial blood stream infections (BSI) caused by MDR *A. baumannii* and hospitalized in General Intensive Care (GICU) and Neurology-Neurosurgery Intensive Care (NNICU) Units of Ankara Atatürk Training and Research Hospital between 01 January 2007 – 31 December 2010.

2.1. Patients

Forty-one patients with diagnosis of nosocomial BSI and MDR *A. baumannii* detected in the blood culture were enrolled as the patient group. Forty-five patients who were hospitalised in the

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same ward in the same period with the patient group and had positive blood cultures for Gram-negative microorganisms other than *A. baumannii* were accepted as control group. Patient characteristics were retrospectively scanned and recorded to study forms.

2.2. Definitions

When a patient had at least one of the clinical findings of fever (38.0 °C), chills or hypotension at least 48 hours after hospitalization, *A. baumannii* was isolated in at least one of the blood cultures obtained from a peripheral vein or central catheter and no *A. baumannii* was isolated in any other culture related with other sources of infection, then diagnosis of bacteremia was accepted. Catheter related BSI was considered as primary BSI. *A. baumannii* isolation in blood culture secondary to any other source of infection was considered as secondary BSI.

Multi-drug resistance was defined as the resistance of *A. baumannii* isolates in ≥ 3 antimicrobial category to ≥ 1 agent from antimicrobial groups aminoglycosides, anti-pseudomonal penicillins + beta lactamase inhibitors, extended spectrum cephalosporins, folate pathway inhibitors, penicillins and inhibitors and polymyxin group antimicrobials.

Septic shock was defined as the sepsis state in which persistant hypotension despite fluid replacement (average arterial pressure ≤ 70 mmHg), organ dysfunction and perfusion abnormalities are observed.

Immunosuppression was defined as presence of corticosteroid treatment equivalent to at least 10 mg/day prednisolone for fifteen days, human immunodeficiency virus (HIV) seropositivity, solid organ transplantation, bone marrow transplantation, history of radiotherapy or chemotherapy for an underlying malignancy in last 6 months and presence of acquired immune deficiencies (hypogammaglobulinemia, combined immunodeficiency syndrome).

Previous antimicrobial usage was defined as systemic antimicrobial treatment for at least 72 hours in 30 days before isolation of Gram-negative microorganism in blood culture.

2.3. Microbiological Analysis

Blood cultures were incubated in BACTEC 9050 system and were identified by BD BBL Crystal identification system. Antimicrobial susceptibility profiles were determined by Kirby Bauer Disc Diffusion Method in accordance with Clinical and Laboratory Standarts Institute (CLSI) recommendations.[7] Due to increase in resistance against antimicrobials like cephoperazone sulbactam and netilmisin, colistin susceptibility test also has been added to the profile since, 2010 thus colistin susceptibility was also evaluated in 7 isolates which were isolated in 2010.

2.4. Cost Analysis

Total hospitalization cost was determined by using the central hospital information system and recorded both case and control group patients. Unit cost of antimicrobial agents that were used during bacteremia episode was acquired from hospital purchase department and cost of antimicrobial therapy and hospitalization were calculated in American Dollars(US$).

2.5. Statistical Method

SPSS 15.0 for Windows was used for statistical analysis of the data. The table of numbers was presented for categoric variables while definitive statistics (mean, standart deviation, median, minimum, maximum) were presented for numerical variables. In order to make paired categorical comparisons, Chi square test was used for independent groups with normal distribution while Fisher's exact test was used for independent groups with no normal distribution. For numerical comparions, t test was used in independent groups with normal distribution while Mann Whitney U test was used in independent groups without normal distribution. Regression analysis of infection and mortality related risk factors was performed by using Forward-Stepwise method. Kaplan Meier test was also used for survival analysis and Backward-stepwise, forward stepwise methods and cox regression analysis were used to determine the risk factors affecting survival rate. A p value less than 0.05 was accepted to be statistically significant.

3. Results

In this study, case group was comprised of 41 patients (23 female, 18 male), of which the mean age was 58.3 ± 21.9 years while the control group had 45 patients (16 female, 29 male) whose mean age was 60.6 ± 20.5 years.

When the case group was evaluated, the percentages of patients in case and control groups with concomitant MDR *A. baumannii* infection other than BSI were 78% and 34%, respectively.

Univariate analysis revealed that the presence of an arterial catheter, high SAPS II score, low serum albumin level, antibiotic treatment with carbapenem, quinolone, metronidazole, glycopeptides and aminoglycosides prior to BSI were the risk factors for MDR *A. baumannii* BSI (Table 1, Table 2).

In multivariate analysis, it was detected that antibiotic treatment with carbapenem (odds ratio (OR) 11.96; 95% confidence interval(CI) 3.31- 43.3; $p < 0.001$), quinolone (OR 6.71; 95% CI 1.31 – 34.40; $p = 0.02$), metronidazole (OR 1.06; 95% CI 2.59 – 391.22; $p = 0.007$) prior to diagnosis of MDR Acinetobacter BSI and SAPS II score (OR 1.06; CI 1.01 – 1.11; $p = 0.1$) were the independent risk factors for MDR *A. baumannii* infection (Table 3).

Crude mortality rate in the case group was 53.7% while 14-day and 28-day mortality rates were 52.4% and 30%, respectively. Mortality attributed to *A. baumannii* BSI was detected as 24.4%. Mean age of patients who died, immunosuppression rates and SAPS II scores were statistically high in univariate analysis ($p < 0.001$, $p = 0.02$, $p = 0.001$, respectively) (Table 4). In multivariate analysis, immunosuppression (OR 4.67; CI 1.19 – 18.36; $p = 0.02$), SAPS II score (OR 0.1.10; CI 1.09 – 1.16; $p < 0.001$), hospitalization stay until BSI (OR 0.95; CI 0.92 – 0.98; $p = 0.001$) were determined as independent risk factors (Table 4).

The mean hospitalization costs of patients in case and control groups were calculated as US$35277 ± US$31758 and US$26333 ± US$20398, respectively and no significant difference was detected between them ($p = 0.282$). Mean costs of antibiotics were calculated for alive patient from each group and were US$1052 ± US$613 and US$836 ± US$567 for case and control groups, respectively. There was no significant difference between the two groups with respect to the cost of antibiotics ($p = 0.249$).

4. Discussion

Nosocomial A. *baumannii* infections are frequently observed especially in intensive care units. Besides being resistant to many antimicrobial agents, this microorganism also has the potential to develop resistance against many antimicrobials during treatment via new mechanisms. In many studies, it was shown that incidence of nosocomial infections caused by MDR *A. baumannii* is increasing worldwide.[8–11]

This study assessed the risk factors for the development of MDR *A. baumannii* BSI, mortality related factors, and cost of this clinical picture. Risk factors for MDR *A. baumannii* implicate variables

Table 1
Demographic characteristics of the patients

	Patient n = 41	Control n = 45	p
Gender (n,%)			
Female	23 (56.1)	16 (35.6)	0.056
Male	18 (43.9)	29 (64.4)	
Age (Mean±Std. Dev.)	58.3 ± 21.9	60.6 ± 20.5	0.659
Clinic (n, %)			
GICU	27 (65.9)	30 (66.7)	0.937
NICU	14 (34.1)	15 (33.3)	
Bacteremia (n, %)			
Primary	24 (58.5)	24 (53.3)	0.627
Secondary	17 (41.5)	21 (46.7)	
Diabetes Mellitus (n, %)	10 (24.4)	14 (31.1)	0.488
Chronic Renal Failure (n, %)	4 (9.8)	4 (8.9)	1.000
Heart Failure (n, %)	10 (24.4)	7 (15.6)	0.304
Malignity (n, %)	1 (2.4)	5 (11.1)	0.205
Chronic Obstructive Pulmonary Disease (n, %)	7 (17.1)	10 (22.2)	0.549
Acute Respiratory Distress Syndrome (n, %)	6 (14.6)	6 (13.3)	0.862
Immunosuppression (n, %)	6 (14.6)	6 (13.3)	0.862
Mechanical ventilation (MV)(n, %)	34 (82.9)	39 (86.,7)	0.629
Central Vein catheterization (CVC)(n, %)	39 (95.1)	40 (88.9)	0.437
Arterial catheterization (AC)(n, %)	30 (73.2)	21 (46.7)	**0.01**
Peripheral Venous Catheterization (n, %)	4 (9.8)	6 (13.3)	0.741
Total Parenteral Nutrition (n, %)	22 (53.7)	26 (57.8)	0.701
Nasogastric tube (n, %)	18 (43.9)	18 (40.0)	0.714
Urinary catheter (n, %)	41 (100.0)	44 (97.8)	1.000
Hospitalization time before BSI(Mean ± Std.Dev.)	25.49 ± 21.47	22.80 ± 19.28	0.429
CVC day before BSI (n, %)	17.02 ± 17.04	18.40 ± 16.51	0.700
MV day before BSI (n, %)	17.24 ± 17.68	19.69 ± 20.20	0.879
Septic shock (n, %)	12 (29.3)	6 (13.3)	007
Prior surgical operation (n, %)	16 (39.0)	14 (31.1)	0.442
SAPS II (Mean ± Std.Dev)	55.20 ± 14.4	48.4 ± 12.4	**0.02**
Albumin (Mean ± Std.Dev)	2.70 ± 0.45	2.85 ± 0.33	**0.02**
Creatinin (Mean ± Std.Dev)	1.30 ± 1.00	1.54 ± 1.46	0.652
Proper empirical treatment (n, %)	13 (31.7)	4 (8.9)	**0.008**

Table 2
Antibiotics used before BSI was diagnosed

Antibiotics	Patient (n,%) (n = 41)	Control (n,%) (n = 45)	p value
Carbapenem	23 (56.1)	7 (15.6)	**<0.001**
3rd generation cephalosporin	22 (53.7)	19 (42.2)	0.289
Aminoglycoside	22 (53.7)	9 (20.0)	**0.001**
Glicopeptide	15 (36.6)	7 (15.6)	**0.02**
Piperacillin tazobactam	14 (34.1)	10 (22.2)	0.218
First generation cephalosporin	9 (22.0)	13 (28.9)	0.461
Quinolone	9 (22.0)	3 (6.7)	**0.04**
Metronidazole	8 (19.5)	1 (2.2)	**0.01**
Sulbactam-ampicillin	7 (17.1)	11 (24.4)	0.401
Linezolide	3 (7.3)	4 (8.9)	1.000

Table 3
Risk factors which are estimated by regression analysis for multi drug resistant *A. baumannii* bacteremia

	P	OR	%95 CI	
Carbapenem	**<0.001**	11.96	3.31	43.30
Quinolone	**0.02**	6.71	1.31	34.40
Metronidazole	**0.007**	31.85	2.59	391.22
SAPS II	**0.01**	1.06	1.01	1.11

OR: Odds ratio, CI: Confidence interval.

Table 4
Mortality related risk factors determined in the case group by regression analysis

	P	OR	%95 CI	
Immunosupression	**0.02**	4.67	1.19	18.36
SAPS II	**<0.001**	1.10	1.04	1.16
Hospitalisation time prior to BSI	**0.001**	0.95	0.92	0.98

OD: Odds ratio, CI: Confidence interval.

related to host defense, invasive procedures, infection control measures, underlying disease, exposure to antibiotics. The factors in our patient grup include high SAPS II score, low serum albumin level, previous antibiotic therapy including carbapenem, aminoglycosides, glycopeptides, quinolone and metronidazole, arteriel catheterization.

Several investigators have found a relationship between multidrug resistance and invasive procedures. In these studies it was shown that invasive mechanical ventilation, central venous catheterization, urinary catheterization and nasogastric tube is a risk factor for multi-drug resistance.[12–15] In contrast, in our study, arterial catheter was determined as a risk factor among invasive procedures. It gives rise to thought the difference of risk factors between different studies may be related with the inter-institutional difference in the compliance to infection control precautions.

It is known that in order to start early, proper antibiotic treatment is very important in ICUs. In two studies, authors showed that the percentage of proper antimicrobial treatment was much lower in patients with MDR *A. baumannii* infection.[16,17] In our study, proper empirical antibiotic treatment rate was significantly high for patients in A. baumannii bacteremia arm ($p = 0.018$). The presence of the same pathogen as infection agent in more than one patient in a ward may affect the choice of empirical treatment, it may be possible that empirical treatment might be started in our study population by taking a possible MDR *A. baumannii* into account.

One of the most important factor underlying antimicrobial resistance of *A. baumannii* infections is long term treatment of the infection with a broad spectrum antibiotics. Our results showed that prior antibiotic treatment by using carbapenem, quinolone, aminoglycoside, glycopeptide and metronidazole is a risk factor for MDR *A. baumannii* bacteremia. This result was compatible with other studies.[5,18–21] In order to prevent development of resistance aganist antimicrobials, these agents must be used for right therapeutic indications for a suitable treatment period.

In multivariate analysis, antibiotic treatment with carbapenem, quinolone, metronidazole prior to bacteremia and SAPS II score were found to be independent risk factors. When literature was searched, it was observed that, in a clinical study which was performed in our country and in which imipenem susceptible and resistant *A. baumannii* infections were compared, hospitalization time prior to infection and prior antibiotic usage were identified as risk factors.[12] In another study, *A. baumannii* colonization and bacteremia were compared and regression analysis revealed that respiratory failure, presence of a central venous catheter, antibiotic usage prior to infection were independent risk factors.[10] Another study in which bacteremias caused by *A. baumanni* and by other causative agents were compared showed that immunosuppression, hospitalization through emergency unit, respiratory failure during hospitalization, prior antibiotic agent consumptions were independent risk factors.[13]

Crude mortality rate for infections caused by MDR *A. baumannii* is high and different percentages are reported (26-58%) in the literature.[22,23] Besides studies reporting that *A. baumannii* itself increases the mortality, however, there are some studies which claim that mortality increase is mostly related with underlying disease and *A. baumannii* infection, itself is not an independent risk

factor which affects mortality rate.[14,24,25] Crude mortality rate for our case patient group was 53%. No statistically significant difference between case and control groups were detected for 14-day and 28-day mortality rates. This situation is claimed to be related with high rate of proper empirical antimicrobial therapy in our case group. In our study, immunosuppression, SAPS II score and hospitalization prior to BSI were defined as independent risk factors for mortality. Immunosuppression was a risk factor for mortality in our case group and it was observed that survival rates were statistically lower in immunosuppressive patients. Besides increasing the mortality, immunosuppression has also a negative effect on survival rate, as well.

Studies focusing on cost effectiveness analysis of *A. baumannii* bacteremia are very rare and these studies show that cost of this infection is much higher. In one of these studies, Lee *et. al.* figured out that mean hospitalization cost and cost of antibiotics were higher in infections caused by resistant *A. baumannii*.[14] The comparative cost analysis of MDR *A. baumannii* bacteremia and bacteremias caused by other Gram-negative agents revealed no significant differences in total hospitalization cost and cost of antibiotics. As mentioned before, this result was related with choice of control group patients in prior study from susceptible bacteremia patients. In a review, it was shown that hospital costs attributable to multi-drug resistance are alarmingly high.[26]

Finally, patients in ICU are under great risk of resistant nosocomial infections. When risk factors for multidrug resistance which were evaluated in our study are considered, it is obvious that some of these can be preventable. The decision for invasive procedures and necessity of invasive equipments must be decided on the basis of individual patient so that unnecessary practices can be avoided. Proper antimicrobial agent must be used for an optimum period and care must be given to prevent unnecessary antibiotic usage. It is important to treat infection with a proper antibiotic as soon as possible, especially in infections caused by MDR microorganisms and in which treatment options are limited.

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