Original Research

Comparison of Risk Factors and Outcomes in Carbapenem-Resistant and Carbapenem-Susceptible Gram-Negative Bacteremia

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Abstract

Background: Carbapenem-resistant Gram-negative bacteremia (CR-GNB) is seen with increasing frequency and result in high mortality. The aim of this study was to compare the risk factors and results of carbapenem-resistant and carbapenem-susceptible Gram-negative bacteremia and to determine the factors related to mortality.

Methods: The study was conducted as a retrospective observational comparative case series between June 2016 and November 2017 in Şişli Hamidiye Etfal Training and Research Hospital. The patients were divided into two groups as carbapenem-susceptible and carbapenem-resistant according to antibiotic susceptibility data of blood cultures. The risk factors for the development of carbapenem resistance, length of hospital stay, mortality rates, and mortality related factors were investigated between these two groups.

Results: Two hundred and eleven cases were included in the study. Of these cases, 54 were resistant to carbapenem and 157 were susceptible to carbapenem. Mortality occurred in 60 (28.4%) patients. The 14 and 28 day mortality rates of patients with carbapenem resistance were significantly higher than those without carbapenem resistance. There was no statistically significant difference between two groups in length of stay in the hospital after bacteremia. Pittsburgh bacteremia score, cardiovascular disease, urinary catheterization, and inappropriate empirical antibiotic therapy were the most significant risk factors for mortality.

Conclusions: Carbapenem resistance is associated with increased mortality and inappropriate empirical antibiotic treatment increases mortality. Therefore, patients should be evaluated for risk factors in predicting CR-GNB and treatment for resistant pathogens should be applied in appropriate patients.

Keywords: Bacteremia; carbapenem-resistant; gram-negative; mortality: risk factors.

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Introduction

Bacteremia is a common condition that causes severe systemic infection and must be treated early. It can progress with high mortality and morbidity. Blood culture plays an important role in the diagnosis of bacteremia. While Gram-positive bacteria have been among the leading causes of bacteremia in recent years, Gram-negative bacteria and especially *Enterobacteriaceae* are the dominant pathogens isolated from blood cultures at the present time.[1,2] Multidrug-resistant Gram-negative infections are increasingly common.[3]

Carbapenems are beta-lactam class antibiotics that inhibit cell wall synthesis by binding to most high molecular-weight penicillin-binding proteins. They are active against a broad range of Gram-positive and Gram-negative aerobic and anaerobic bacteria due to their efficient penetration through the bacterial outer membrane, high affinity for multiple penicillin-binding proteins.[4] Carbapenems have been playing an important role in the treatment of infections with Gram-negative bacteria since their first discovery. They are often used when there is no other option, especially for infections with resistant pathogens. Increased resistance rates to carbapenems affect patient prognosis and constitute an important economic burden.[5,6] To emphasize the importance of the issue on public health, the Centers for Disease Control and Prevention described carbapenem-resistant *Enterobacteriaceae* as an important threat,[7] The World Health Organization stated that antibiotic development should be given priority to carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.[8]

The aim of this study was to determine the distribution of pathogens, risk factors for the development of carbapenem resistance, to compare the results of carbapenem resistant and susceptible infections and to determine the factors associated with mortality in patients with Gram-negative bacteremia (GNB).

Materials and Methods

The study was conducted as a retrospective observational comparative case series between June 2016 and November 2017 in Şişli Hamidiye Etfal Training and Research Hospital. First episodes of adult male and female patients (over 18 years of age) who were hospitalized in our hospital with Gram-negative bacterial growth as a causative agent of infection in blood culture were included in the study. Patients with more than one bacterial growth in the blood culture, patients younger than 18 years and pregnant women were excluded from the study. Demographic,

clinical, and laboratory data of the cases were analyzed. Patients were divided into two groups as carbapenem-susceptible GNB (CS-GNB) and carbapenem-resistant GNB (CR-GNB) according to the antibiotic susceptibility of pathogens. Among these two groups, risk factors for the development of carbapenem resistance, length of stay in the hospital after bacteremia, all-cause mortality rates and factors associated with mortality were investigated. The study was approved by the ethics committee of our institution with the document no 906 dated December 26, 2017.

Blood cultures were studied in the clinical microbiology laboratory using an automated blood culture system (BACTEC 9240, Becton Dickinson, U.S.A.). Bacteria isolated from blood culture were identified using BD Phonenix (Becton Dickinson, U.S.A.) and MALDI-TOF MS (Bruker, Germany). Antimicrobial susceptibility results were determined using Kirby–Bauer disc diffusion method and BD Phonenix automated system according to EUCAST criteria. Samples with resistant or reduced susceptibility to one of the carbapenems in either of these two methods were further evaluated for carbapenem resistance by gradient strip test (E-test, bioMerieux, Marcy I'Etoile, France). Cases found to be resistant to any or all of ertapenem, meropenem or imipenem were included in the carbapenem resistant group. For bacteria with intrinsic ertapenem resistance (*Pseudomonas* spp. and *Acinetobacter* spp.) those resistant to either or both imipenem and meropenem were included in the carbapenem-resistant group.

Charlson comorbidity index was used to determine the severity of comorbidity. This method predicts 10-year survival in patients with multiple comorbidities. Estimated 10-year survival significantly decreases with values of 5 and above.[9] The Pittsburgh bacteremia score was used to determine disease severity. This score system is commonly used as a predictor of early mortality risk in patients with bloodstream infections. It ranges from 0 to 14 points, with a score ≥4 commonly used as an indicator of critical illness and increased risk of death.[10] Antibiotic use before infection development was defined as the use of antibiotics for at least 2 days in the past 30 days. Prior intensive care unit admission and prior hospitalization were investigated for the past 3 months. Empirical antibiotic therapy was defined as antibiotic therapy that was started on the same day after blood culture was taken. Empirical antibiotic therapy was considered as appropriate empirical antibiotic therapy if it contains at least one *in vitro* susceptible agent for the pathogen and inappropriate empirical antibiotic therapy if

not. All-cause mortality was evaluated for 14 and 28 days after bacteremia.

Statistical Analysis

Statistical analysis was performed using the SPSS version 15.0 for statistical software package (IBM, NY). In the descriptive statistics, mean, and standard deviation were used to summarize the continuous variables and number, frequency and proportion were used to summarize the categorical variables. For the comparison of continuous variables in two independent groups, Mann–Whitney U-test was used when appropriate. Chi-square test was used in comparison of categorical variables. Determinants were examined by logistic regression analysis. $p<0.05$ was regarded as indicative of statistical significance.

Results

During the study period, the first episode GNB was detected for 365 patients and 154 cases were excluded due to lack of data, multiple growth in blood culture, pregnancy, and under 18 years of age. A total of 211 cases were included in the study. Ninety eight (46.4%) of the patients were female and 113 (53.6%) were male. The mean age was 68.1±17 years. Forty-six (21.8%) of patients was at intensive care unit.

The most common microorganisms were *Escherichia coli* (n=88), *Klebsiella pneumoniae* (n=54). The microorganism with the highest carbapenem resistance rate was *Acinetobacter* spp (94.4%). One hundred and fifty seven of the cases were evaluated as CS-GNB and 54 of them were evaluated as CR-GNB (Table 1).

Table 1. Distribution of microorganisms

Microorganism	Total *n* (%)	CS-GNB *n* (%)	*CR-GNB* *n* (%)
Escherichia coli	88 (41.7)	86 (97.7)	2 (2.3)
Klebsiella pneumoniae	54 (25.6)	40 (74)	14 (26)
Acinetobacter spp.	36 (17.1)	2 (5.6)	34 (94.4)
Pseudomonas spp.	13 (6.2)	11 (84.6)	2 (15.4)
Stenotrophomonas maltophilia	2 (0.9)	0 (0)	2 (100)
Enterobacter spp.	11 (5.2)	11 (100)	0 (0)
Morganella morganii	4 (1.9)	4 (100)	0 (0)
Proteus mirabilis	2 (0.9)	2 (100)	0 (0)
Serratia marcescens	1 (0.5)	1 (100)	0 (0)
Total	211	157	54

CR-GNB: Carbapenem-resistant Gram-negative bacteremia; CS-GNB: carbapenem-susceptible Gram-negative bacteremia.

There was no significant difference between the groups in terms of age and gender. The most common underlying diseases were diabetes mellitus (n=69), malignancy (n=57), and chronic renal failure (n=54). The most common invasive procedure was urinary catheterization (n=84). Beta-lactam/beta-lactamase inhibitors (n=38) and cephalosporins (n=28) were the two most common antibiotic groups used prior to infection (Table 2).

The 14 and 28-day mortality rates of CR-GNB patients were significantly higher than CS-GNB patients ($p<0.001$ for both). There was no statistically significant difference between the two groups in terms of length of stay in the hospital after bacteremia (Table 3).

In the univariate analysis conducted to investigate the factors associated with mortality, the mean Pittsburgh bacteremia score, the rate of prior intensive care unit admission, the rate of antibiotic use in the last 30 days, the rate of total parenteral nutrition, previous surgery rate, mechanical ventilation rate, central venous catheterization rate, and urinary catheterization rate were significantly higher in patients with mortality. The rate of inappropriate empirical antibiotic therapy was statistically higher in patients with mortality. In comparison of *Enterobacteriaceae* and non-*Enterobacteriaceae* microorganisms in terms of mortality, it was found that the cases with mortality were mostly from the *Enterobacteriaceae* family (Table 4).

Logistic regression analysis was performed by forming a model with the variables determined as $p<0.250$ in the univariate analysis above to determine the factors associated with mortality. In this model, there were Charlson comorbidity index, Pittsburgh bacteremia score, prior intensive care unit admission, antibiotic use in the past 30 days, congestive heart failure, diabetes mellitus, cardiovascular disease, cerebrovascular disease, total parenteral nutrition, previous surgery, mechanical ventilation, central venous catheterization, urinary catheterization, inappropriate empirical antibiotic therapy, and being in the non-enterobacteriaceae family variables. Pittsburgh bacteremia score, cardiovascular disease, urinary catheterization, and inappropriate empirical antibiotic therapy were the most significant risk factors for mortality (Table 5).

Discussion

Bacteremic infections are important because of the high mortality rate among hospitalized patients. Among these infections, those caused by Gram-negative bacteria remain the most frequent.[11] Considering the time it takes to obtain blood culture results, it is of great importance to realize which patients may be resistant pathogens to provide appropriate antimicrobial therapy. Infections with

Table 2. Demographics, clinical characteristics of the GNB patients

Characteristic	Total	CS-GNB	CR-GNB	P
Female, n (%)	98 (46.4)	69 (43.9)	29 (53.7)	0.215
Male, n (%)	113 (53.6)	88 (56.1)	25 (46.3)	
Age, mean day±SD	68.1±17.0	68.2±16.8	67.7±17.9	0.796
Length of stay, mean day±SD	26.4±32.7	20.0±21.2	45.1±49.3	<0.001
Length of stay before infection, mean day±SD	9.3±19.7	5.4±12.6	20.6±30.0	<0.001
Charlson comorbidity index, mean±SD	5.4±2.8	5.4±2.7	5.3±3.0	0.748
Pittsburgh bacteremia score, mean±SD	2.8±3.0	2.1±2.8	4.8±2.8	<0.001
Prior intensive care unit admission, n (%)	63 (29.9)	21 (13.4)	42 (77.8)	<0.001
Prior hospitalization, n (%)	112 (53.1)	67 (42.7)	45 (83.3)	<0.001
Antibiotic use in the past 30 days, n (%)	90 (42.7)	48 (30.6)	42 (77.8)	<0.001
Previously used antibiotic				
Beta-lactam/beta-lactamase inhibitor, n (%)	38 (18)	18 (11.5)	20 (37)	<0.001
Cephalosporins, n (%)	28 (13.3)	17 (10.8)	11 (20.4)	0.075
Carbapenems, n (%)	10 (4.7)	2 (1.3)	8 (14.8)	<0.001
Fluoroquinolones, n (%)	13 (6.2)	10 (6.4)	3 (5.6)	1.000
Tigecycline, n (%)	5 (2.4)	0 (0)	5 (9.3)	<0.001
Trimethoprim-sulfamethoxazole, n (%)	2 (0.9)	1 (0.6)	1 (1.9)	0.447
Comorbidity				
Chronic renal failure, n (%)	54 (25.6)	42 (26.8)	12 (22.2)	0.511
Hemodialysis, n (%)	22 (10.4)	16 (10.2)	6 (11.1)	0.849
COPD, n (%)	15 (7.1)	10 (6.4)	5 (9.3)	0.540
Congestive heart failure, n (%)	22 (10.4)	15 (9.6)	7 (13)	0.480
Chronic liver disease, n (%)	9 (4.3)	9 (5.7)	0 (0)	0.116
Diabetes mellitus, n (%)	69 (32.7)	48 (30.6)	21 (38.9)	0.261
Cardiovascular disease, n (%)	53 (25.1)	41 (26.1)	12 (22.2)	0.569
Cerebrovascular disease, n (%)	35 (16.6)	16 (10.2)	19 (35.2)	<0.001
Malignancy, n (%)	57 (27)	43 (27.4)	14 (25.9)	0.835
Immunosuppressive treatment, n (%)	25 (11.8)	23 (14.6)	2 (3.7)	0.032
Transplantation, n (%)	4 (1.9)	3 (1.9)	1 (1.9)	1.000
Urolithiasis, n (%)	13 (6.2)	12 (7.6)	1 (1.9)	0.191
Home healthcare, n (%)	16 (7.6)	11 (7)	5 (9.3)	0.562
Total parenteral nutrition, n (%)	19 (9)	5 (3.2)	14 (25.9)	<0.001
Prior invasive procedures				
Surgery, n (%)	49 (23.2)	25 (15.9)	24 (44.4)	<0.001
Mechanical ventilation, n (%)	54 (25.6)	17 (10.8)	37 (68.5)	<0.001
Central venous catheterization, n (%)	68 (32.2)	30 (19.1)	38 (70.4)	<0.001
Urinary catheterization, n (%)	84 (39.8)	37 (23.6)	47 (87)	<0.001

CR-GNB: Carbapenem-resistant Gram-negative bacteremia; CS-GNB: Carbapenem-susceptible Gram-negative bacteremia; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease.

Table 3. Outcomes of patients with GNB

	Total	CS-GNB	CR-GNB	P
Length of stay in the hospital after bacteremia, mean day±SD	17.2±21.7	14.6±14.0	24.5±34.8	0.340
14-day mortality, n (%)	42 (19.9)	21 (13.4)	21 (38.9)	<0.001
28-day mortality, n (%)	60 (28.4)	31 (19.7)	29 (53.7)	<0.001

Table 4. Univariate analysis for predictors of 28-day mortality

Variable	Died (n=60)	Survived (n=151)	P
Female, n (%)	26 (43.3)	72 (47.7)	0.568
Male, n (%)	34 (56.7)	79 (52.3)	
Age, mean day±SD (Median)	70.9±14.9 (70.5)	67.0±17.7 (71)	0.328
Charlson comorbidity index, mean±SD	6.0±2.7	5.1±2.8	0.097
Pittsburgh bacteremia score, mean±SD	6.1±3.0	1.5±1.8	<0.001
Prior intensive care unit admission, n (%)	32 (53.3)	31 (20.5)	<0.001
Prior hospitalization, n (%)	37 (61.7)	75 (49.7)	0.115
Antibiotic use in last 30 days, n (%)	34 (56.7)	56 (37.1)	0.009
Chronic renal failure, n (%)	14 (23.3)	40 (26.5)	0.635
Hemodialysis, n (%)	7 (11.7)	15 (9.9)	0.710
COPD, n (%)	6 (10.0)	9 (6.0)	0.373
Congestive heart failure, n (%)	9 (15.0)	13 (8.6)	0.171
Chronic liver disease, n (%)	4 (6.7)	5 (3.3)	0.277
Diabetes mellitus, n (%)	24 (40.0)	45 (29.8)	0.154
Cardiovascular disease, n (%)	19 (31.7)	34 (22.5)	0.167
Cerebrovascular disease, n (%)	14 (23.3)	21 (13.9)	0.097
Malignancy, n (%)	17 (28.3)	40 (26.5)	0.786
Immunosuppressive treatment, n (%)	6 (10.0)	19 (12.6)	0.601
Transplantation, n (%)	1 (1.7)	3 (2.0)	1.000
Total parenteral nutrition, n (%)	11 (18.3)	8 (5.3)	0.003
Surgery, n (%)	23 (38.3)	26 (17.2)	0.001
Mechanical ventilation, n (%)	27 (45.0)	27 (17.9)	<0.001
Central venous catheterization, n (%)	30 (50.0)	38 (25.2)	<0.001
Urinary catheterization, n (%)	38 (63.3)	46 (30.5)	<0.001
Appropriate empirical antibiotic therapy, n (%)	25 (41.7)	107 (70.9)	<0.001
Inappropriate empirical antibiotic therapy, n (%)	35 (58.37)	44 (29.19)	
Enterobacteriaceae, n (%)	38 (63.3)	122 (80.8)	0.008
Non-enterobacteriaceae, n (%)	22 (36.7)	29 (19.2)	

carbapenem-resistant bacteria are increasing in frequency, especially in patients with chronic and severe diseases.[5,12] Antibiotic options for treatment are limited. Despite appropriate and adequate treatments, high mortality rates are observed in carbapenem-resistant infections.[13]

Distribution of pathogens and antibiotic resistance rates in bloodstream infections may vary according to the antibiotic treatment protocols, geographical location, and whether or not nosocomial infection. According to the data from literature, the most common causes of GNB are *E. coli*, *K. pneumoniae*, *Acinetobacter* spp., and *Pseudomonas* spp.[14,15] Similar to these results, in our study, *E. coli*, *K. pneumoniae*, *Acinetobacter* spp., and *Pseudomonas* spp. were the microorganisms detected in order of frequency.

It is important to predict risk factors for carbapenem resistance. There are many studies in the literature showing

Table 5. Logistic regression analysis of risk factors associated with 28-day mortality

Variable	P	Odds ratio	%95 Confidence Interval
Pittsburgh bacteremia score	<0.001	3.766	2.482–5.712
Cardiovascular disease	0.008	5.292	1.532–18.280
Urinary catheterization	0.009	6.307	1.579–25.182
Inappropriate empirical antibiotic therapy	0.019	3.398	1.223–9.440

risk factors related to carbapenem resistance in various GNB. Considering the results of these studies, the use of antipseudomonal penicillin, antipseudomonal cephalosporin or carbapenem in the past 30 days and long hospitalization period before bacteremia,[16] history of intensive care unit admission, cefoperazone-sulbactam or carbapenem use within the past 30 days,[17] central venous catheterization, mechanical ventilation, hospitalization before infection, use of carbapenem, aminoglycoside or tigecycline in the past 30 days and high Pittsburgh bacteremia score,[18] carbapenem use, intensive care unit admission, central venous catheterization, chronic liver disease, dialysis, and mechanical ventilation[19] were identified as risk factors for the development of carbapenem-resistant infection. In our study, similar to other studies, the length of hospital stay before infection, intensive care unit or hospital stay within the past 3 months, the use of beta-lactam/beta-lactamase inhibitor or carbapenem in the past 30 days, high Pittsburgh bacteremia score, mechanical ventilation, and central venous catheterization were associated with carbapenem-resistant infection. In addition, the presence of cerebrovascular disease, total parenteral nutrition, previous surgery, and urinary catheterization were identified as factors associated with carbapenem resistance. Cephalosporin use, hemodialysis, and presence of chronic obstructive pulmonary disease (COPD) were found to be higher in the carbapenem-resistant group like in other studies, but no statistically significant difference was found in our study.

In the literature, there are many studies investigating the effects of the carbapenem resistance, and in the majority of them, it has been shown that carbapenem resistance results in increased mortality for Gram-negative bacterial infections.[16,18,20,21] Mortality rates in our study were similar to the data in the literature and 14-day and 28-day mortality rates were significantly higher in the CR-GNB group. Independent risk factors for mortality were high Pittsburgh bacteremia score, presence of cardiovascular disease, urinary catheterization, and inappropriate empirical antibiotic

therapy. In some studies, length of stay in the hospital after bacteremia was significantly higher in the carbapenem-resistant Gram-negative infections compared to carbapenem-susceptible infections.[16,19,20] However, no significant difference was found between these two groups in terms of length of stay in the hospital after bacteremia in our study.

There are many studies in the literature showing the relationship between appropriate empirical antibiotic therapy and mortality; however, there are different conclusions about this relationship. In a study involving carbapenem-resistant *Enterobacteriaceae* bacteremia, appropriate empirical antibiotic therapy was found to be a factor reducing mortality.[22] In an another study of 1076 intensive care patients with GNB, inappropriate empirical antibiotic therapy was found to be the most important risk factor associated with mortality.[23] However, in a study involving 679 GNB patients, advanced age, comorbid diseases, and disease severity at admission were found to be independent risk factors associated with mortality, but inappropriate empirical antibiotic therapy was not a risk factor.[24] Similar results were found in our study, and inappropriate empirical antibiotic therapy was found to be a significant risk factor for mortality. The Pittsburgh bacteremia score is an important predictor of disease severity in bloodstream infections. In our study, similar to the literature, high Pittsburgh bacteremia score was found to be an independent risk factor associated with mortality. Other risk factors associated with mortality were cardiovascular disease and urinary catheterization.

The retrospective nature of our study, lack of evaluation of effects of various antibiotic regimens on outcomes and the lack of molecular methods to investigate carbapenemase types were considered as limitations.

In summary, carbapenem resistance was found to be associated with high mortality in our study. Appropriate empirical antibiotic therapy and urinary catheterization are important because they are modifiable. To predict carbapenem resistance, it is important to question patients in terms of risk factors. It was thought that mortality could be reduced by evaluating risk factors for resistant pathogens and initiating appropriate empirical antibiotic treatment.

Disclosures

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Conflict of Interest: None declared.

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