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Original Article

Risk Factors and Outcomes for Carbapenem-resistant Klebsiella Pneumoniae Infection in Haematological Patients

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ABSTRACT

Background Prolonged hospitalization, prolonged neutropenia, and immunosuppressive treatments increase bloodstream infections in haematological patients. Identifying risk factors for carbapenem-resistant Klebsiella pneumoniae (CRKP) infection will shed light on controlling the spread of CRKP. Our retrospective study aimed to determine the clinical features, antimicrobial susceptibility, and mortality risk factors of patients who developed CRKP in patients followed up for haematological cancer in the Izmir University of Economics Haematology Department.

Material and Methods 19,170 blood-urine-sputum cultures were delivered from the patients, 1,595 (8.31%) of which presented growth. CRKP comprised 302 (1.57%) of such growth cases. The study included 72 patients with haematological malignancy who presented CRKP growth in 302 cultures obtained during the neutropenic fever period.

Results The mean age of patients was 51 (18-75 years). Acute myeloid leukaemia was the most common disease (n: 26, 36.11%). As to the antibiotic sensitivity of CRKP, 44 patients (61.1%) were colistin sensitive, 28 patients (38.9%) were colistin-resistant, 47 patients (65.3%) were tigecycline sensitive/medium sensitivity, 25 patients (34.7%) were tigecycline resistant, there was no statistically significant difference between antibiotic sensitivities and survival.

Conclusions Today, early detection of CRKP colonization in high-risk haematological patients, taking rectal culture, and if the patient presents rectal colonization of CRKP or had CRKP bacteremia during prior hospitalizations, early initiation of treatment with antibiotics acting against CRKP during NPF would significantly reduce mortality.

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INTRODUCTION

In recent years, total life expectancy in haematological patients has been extended by the development of effective chemotherapy treatments, increased frequency of autologous and allogeneic stem cell transplantation, and improved supportive treatments. However, prolonged hospitalization, long neutropenia time, invasive medical procedures and repeated intensive immunosuppressive treatments increase bloodstream infections.[1] The frequency of bloodstream infection among cancer patients varies between 11% and 38%, and the mortality rate rises to 40%.[2] Carbapenems (meropenem or imipenem/cilastatin) are used in the first place in hemodynamically unstable patients with neutropenic fever, comorbid diseases, and neutrophil < 100/mm3.[3,4] The use of long-term carbapenem increases the prevalence of meropenem-resistant gram-negative bacteria. Multi-drug-resistant (MDR) gram-negative bacteria are reported at an increasing rate in many countries worldwide.[5] The most frequently isolated factor in carbapenem-resistant bacterial infections is *Klebsiella pneumoniae*.[6] Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is one of the nosocomial pathogens that can cause outbreaks where high mortality rates are observed and frequently isolated, especially from intensive care patients.[7] CRKP bacteremia is also a bacterium with increasing prevalence and can cause significant morbidity and mortality in immunosuppressed patients. In this group of patients, prolonged use of broad-spectrum antibiotics during neutropenic fever increases the frequency of colonization of MDR gram-negative bacteria in different body parts.

The control and treatment of CRKP is a critical problem worldwide and in Turkey.[8] CRKP's MDR and limited antibiotic responsiveness reduce the chances of treatment.[9,10] The optimal treatment approach for Enterobacteriaceae infections with carbapenem-resistance has not yet been determined. Treatment options for *Enterobacteriaceae* infections resistant to carbapenem include polymyxin B, colistin, tigecycline, fosfomycine, aminoglycosides and ceftazidime-avibactam.[11] With its bactericidal effect depending on concentration and ability to reach an adequate concentration in serum, colistin represents an important treatment option, especially in CRKP infections in blood circulation.[12] With the widespread use of colistin, colistin-resistance has increased.[13,14] Determining the risk factors for CRKP infection will shed light on controlling the spread of CRKP. In patients with a haematological malignancy, there is limited information on the epidemiology of *Klebsiella pneumoniae* bacteremia, development risk factors, and disease prognosis. In our retrospective study, we aimed to identify the clinical characteristics, laboratory findings, antimicrobial sensitivities, disease development and mortality risk factors of patients that developed CRKP among those who have been followed up in the Izmir University of Economics, Faculty of Medicine, Haematology Department with haematological cancer, who received chemotherapy or underwent allogeneic or autologous stem cell transplantation.

MATERIAL AND METHODS

In this retrospective study, among the patients who were hospitalized and followed up at the Haematology Clinic and Bone Marrow Transplantation Unit of Izmir University of Economics, Faculty of Medicine from 1 January 2015 to 31 August 2019, the patients who presented single or repeated CRKP growth through the neutropenic period in catheter and/or peripheral blood, urine and sputum cultures were included. The characteristics of patients, epidemiological and clinical findings, underlying diseases, antimicrobial susceptibility profiles, laboratory findings, and additional interventional procedures were evaluated. The ethics committee approved the study. No informed consent was received from patients due to the study's retrospective design.

Microbiological tests

When the axillary fever of neutropenic patients was >38 °C, the patients' catheter, peripheral blood, urine cultures and sputum cultures (if they presented sputum) were taken. (BACTECTM FX 200, Becton Dickinson). The bacterial identification and antibiotic susceptibility tests were performed with a microflex-TM LT/SH mass spectrometer (Bruker Daltonik, Bremen, Germany) and a VITEK® system (bioMérieux, Hazelwood, MO, USA) according to the manufacturer's instructions. Cefazolin, cefoperazone-sulbactam and tigecycline were determined by the Kirby-Bauer disk diffusion method.

Definitions

It was defined by the Infectious Diseases Society of America.15 This definition defines fever as an axillary temperature of at least 38.3 °C measured at once or above 38 °C continuing for more than an hour. Later, body temperature rising to 38 °C and above twice within 12 hours was added to this definition. According to the 2003 guidelines of the Febrile Neutropenia

Working Group in our country, neutropenic fever is defined as orally measured body temperature > 38.3 °C at once or >38 °C for more than one hour in neutropenic patients.16 Neutropenia is when the absolute number of neutrophils is less than 500/mm^3 or the number of neutrophils initially less than 1,000/mm3 drops to 500/mm^3 or less within 24-48 hours. Septic shock is defined as the condition in which systolic blood pressure is < 90 mmHg for a patient with fever or the need to use inotropic agents to maintain blood pressure at normal levels.

Klebsiella pneumoniae bacteremia was diagnosed when at least one of the blood sample cultures was positive for *Klebsiella pneumoniae.* Empirical antibiotic therapy was considered appropriate if at least one drug was active against the strain of Klebsiella pneumoniae (as determined by in vitro susceptibility tests). Antibiotic susceptibility was determined according to the Clinical and Laboratory Standards Institute 2015 recommendations.[17] MDR was defined as non-susceptible to at least one agent in ≥ 3 antimicrobial categories, according to Magiorakos *et al*.[18] Initial treatment for patients with neutropenic fever starts with meropenem treatment. Then, after CRKP growth, aminoglycosides, colistin and tigecycline were added to the treatment with antibiotics administered according to the antibiogram. If the patient had CRKP infection in previous neutropenic fever periods or rectal CRKP colonization, combined antibiotic therapy was started without waiting for culture in resistant fever.

Statistical Analysis

The data were expressed as mean±SD for normally distributed continuous variables, median (minimum:-maximum) for skew-distributed continuous variables, and frequencies for categorical variables. Pearson's chi-square test was performed to compare the categorical variables. ANOVA compared means of normally distributed continuous variables. The Mann-Whitney U test compared skew-distributed continuous variables. Cox regression analysis was used for multivariate analyses. The Statistical Package for Social Sciences (SPSS) for Windows version 15.0 (SPSS Inc., Chicago) was used for the analysis, and a two-sided *p* - value of <0.05 was considered significant.

RESULTS

Patient Characteristics

Nineteen thousand one hundred seventy blood-urine-sputum cultures were delivered from the patients hospitalized at Izmir University of Economics, Medicalpark Hospital, Clinic of Haematology and Bone Marrow Transplantation Unit, 1,595 (8.31%) of which presented growth. CRKP comprised 302 (1.57%) of such growth cases. The study included 72 patients with haematological malignancy who presented CRKP growth in 302 cultures obtained during the neutropenic fever (NPF) period. Table 1 showed the basic characteristics of 72 patients. The mean age of patients was 51 years (range: 18-75); 50 (69.44%) of them were male, and 22 (30.56%) were female. Acute myeloid leukaemia (AML) was the most common disease (n: 26, 36%). Other diseases were acute lymphoblastic leukaemia (n:18, 25%), non-Hodgkin lymphoma (n: 18, 25%), multiple myeloma (n: 5, 7%), aplastic anaemia (n: 3, 4.16%) and myelodysplastic syndrome (n: 2, 2.84%).

When patients are examined, CRKP growth was observed in 41 patients (56.95%) during remission induction treatment, 9 (12.5%) during consolidation treatment, 7 (9.72%) during peripheral hematopoietic stem cell transplantation, 12 (16.66%) during allogeneic stem cell transplantation, and 3 (4.17%) during hospitalization for acute graft versus host disease (GVHD) treatment. While 47 (65.28%) patients presenting growth had a treatment-resistant disease, 25 (34.72%), patients were in remission. Eight patients received the first remission induction, 16 received the second, 12 received the third, 7 received the fourth, one received the fifth, and three received the sixth induction treatments with resistant diseases. Ten patients had related allogeneic stem cell transplantation, and six underwent unrelated transplantation. Six of the patients with allogeneic transplants underwent transplantation with resistant disease. Six patients had CRKP rectal colonization while undergoing allogeneic transplantation, 12 presented CRKP growth during chemotherapy, and 4 presented it during hospitalization for acute GVHD treatment. CRKP growth was detected in the first month of transplantation in 11 patients, 30-100 days in 3 patients and 100-365 days in 2 patients. Acute GVHD developed in 6 of 15 patients during the follow-up. Five patients were treated with methylprednisolone, and cyclosporine, while one was treated with multiple immunosuppressive treatments (methylprednisolone, mycophenolate mofetil, tacrolimus, and mesenchymal stem cell infusion).

Eight of the ten patients with allogeneic transplants from sibling donors who had CRKP growth during

Table 1. Characteristics of patients and their impact on survival.

Parameters	Subgroup	Survival		P value	χ^2
		Live	Exitus		
Gender	Woman	6	16	0.815	0.055
	Man	15	35		
Diagnosis	Acute myeloid leukaemia*	3	23	0.003	17.743
	Acute lymphoblastic leukaemia	4	14		
	non-Hodgkin lymphoma	7	11		
	Multiple myeloma	5	0		
	Myelodysplastic syndrome	1	1		
	Aplastic anemia	1	2		
Amikacin	Sensitive	2	15	0.125**	3.262
	Resistant	19	36		
Colistin	Sensitive	13	31	0.929	0.008
	Resistant	8	20		
Tigecycline	Sensitive	5	14	0.613	0.979
	Medium sensitivity	10	18		
	Resistant	6	19		
Meropenem	Resistant	21	51	NC	NC
Gentamicin	Sensitive	2	10	0.489**	1.089
	Resistant	19	41		
Chemotherapy	None	1	2	0.002	19.182
	Remission induction*	7	34		
	Consolidation	4	2		
	Autologous SCT	6	1		
	Allogeneic SCT	3	9		
	GVHD treatment	0	3		
Resistant disease	No	12	13	0.010	6.575
	Yes	9	38		
Allogeneic transplantation	None	18	38	0.577	1.101
	Allo-sibling	2	8		
	Allo-unrelated	1	5		
Prior transplantation	No allo-autologous SCT	20	32	0.019	7.932
	Allogeneic SCT	1	13		
	Autologous SCT	0	6		
CRKP growth location	Catheter blood	1	2	0.961	0.081
	Peripheral blood	1	3		
	Catheter-peripheral blood	12	34		
Quinolon oral prophylaxis	None	5	8	0.504**	0.663
	Positive	16	43		
Use of meropenem	No	1	4	1.000**	0.219
	Yes	20	47		
Use of meropenem in the last 4 weeks	No	2	6	1.000**	0.076
	Yes	19	45		
Neutrophil during infection	500-700/mm^3	4	4	0.332	2.205
	<100-500/mm^3	16	42		
	<100/mm^3	1	5		
Transferred from another centre	No	12	21	0.217	1.527
	Yes	9	30		
Hospitalization at ICU	No	20	46	0.664**	0.495
	Yes	1	5		
Invasive procedure	Non-catheter	2	10	0.488**	0.944
	Catheter	18	41		
Mucositis	Grade 1-2	19	43	0.713**	0.472
	Grade 3-4	2	8		
Prior NPF colonization	None	15	45	0.095**	3.025
	Positive	6	6		
Prior NPF bacteremia	None	15	46	0.131**	2.742
	Positive	5	5		
CRKP bacteremia 30-day mortality	None	21	3	< 0.001	59.294
	Positive	0	48		

Continuation of Table 1

Parameters	Subgroup	Survival		P value	χ^2
		Live	Exitus		
Empirical treatment	M	0	1	0.243	9.142
	M-A	1	0		
	M-A-C	0	3		
	M-A-C-T	13	28		
	M-G-C-T	3	5		
	M-C-T	2	13		
	M-C	1	1		
	M-T	1	0		
IPA	None	17	37	0.454	0.560
	Positive	4	14		
IPA Treatment	None	7	17	0.894	0.613
	Caspofungin	11	25		
	Voriconazole	1	4		
	Liposomal amphotericin B	2	7		
Colonization at hospitalization	Unexamined	7	30	0.685**	0.286
	None	10	13		
	Positive	6	6		
GVHD	None	19	43	0.662**	0.515
	Acute GVHD	1	5		
Immunosuppressive treatment	No	16	32	0.322	0.980
	Yes	4	15		
Septic shock	None	13	3	< 0.001**	27.011
	Positive	8	48		
Inhaler treatment	None	17	32	0.132	2.268
	Positive	4	19		
Mechanical ventilation	None	20	20	< 0.001	18.908
	Positive	1	31		
Cause of death	Other	21	38	0.011**	7.430
	Klebsiella bacteremia	0	13		

$P < 0.05$ was considered significant and * indicates significant subgroup. Pearson's Chi-Square and **Fisher's Exact Chi-Square tests were used. NC: not calculated. SCT: stem cell transplantation, GVHD: Graft versus host disease, CRKP: carbapenem-resistant *Klebsiella pneumoniae*, ICU: intensive care unit, NPF: neutopenic fever, M: meropenem, A: amikacin, G: gentamisin, C: colistin, T: tigecycline, IPA: invasive pulmoner aspergillosis.

hospitalization and 5 of the six patients with unrelated transplants were lost at the follow-up. Six of the lost patients with allogeneic transplants underwent transplantation with resistant disease. Twelve patients (16.7%) presented rectal CRKP colonization; ten patients (14.1%) had CRKP bacteremia in previous NPF periods. The patients presenting growth were hospitalized five times on average (1 to 12 times), 39 patients (54.2%) were transferred to our hospital from another clinic, and six patients (8.3%) stayed in the intensive care unit. Sixty patients (83.3%) had a temporary central venous catheter. The most common invasive procedure for patients was the insertion of the temporary central venous catheter, and other less frequent methods were shown in Table 2. CRKP growth was detected in the catheter and peripheral blood cultures in 47 patients (65.28%), peripheral blood culture only in 4 patients (5.5%), and catheter blood culture only in 4 patients (5.5%) (Table 3). On average, CRKP growth was observed to be 1.94 (1-6) for peripheral blood culture and 1.73 (1-5) for catheter blood culture. It was observed that 64 patients (88.9%) with growth have been receiving meropenem in the last four weeks, 67 patients took meropenem due to NPF (93.1%) during growth, while 60 patients (83.3%) received quinolone prophylaxis. On average, they took meropenem for 9.05 days between 0-30 days.

Considering the empirical antibiotic treatments given to this patient group, 41 patients (56.94%) received meropenem, amikacin, colistin, and tigecycline in combination, 15 (20.83%) meropenem, colistin, tigecycline and eight patients (11.1%) took meropenem, gentamycin, colistin treatment (Table 1).

As to the antibiotic sensitivity of CRKP, 44 patients (61.1%) were colistin sensitive (31 patients lost on follow-up, 84%), 28 patients (38.9%) were colistin-resistant (20 patients lost on follow-up, 71%), 47 patients (65.3%) were tigecycline sensitive/medium sensitivity (32 patients lost, 65%), 25 patients (34.7%) were tigecycline resistant (19 patients lost, 76%), 17 patients (23.61%) were amikacin sensitive (15 patients lost, 88%), 55 patients (76.39%) were amikacin resis

Table 2. Distribution of 72 invasive procedures applied to patients.

Procedure	n (%)
Central and venous catheter	60 (83.2)
Endoscopy-colonoscopy	2 (2.8)
Rectal abscess drain	2 (2.8)
Abdomen exploration	2 (2.8)
Splenectomy	1 (1.4)
Bronchoscopy	1 (1.4)
Prostate abscess drain	1 (1.4)
Pancreas cyst drain	1 (1.4)
No procedure	2 (2.8)

Table 3. CRKP growth locations.

Locations	n (%)
Catheter-peripheral blood culture	47 (65.28)
Blood-urine culture	6 (8.3)
Sputum-blood culture	6 (8.3)
Catheter blood culture	4 (5.5)
Peripheral blood culture	4 (5.5)
Urine culture	3 (4.32)
Sputum culture	1 (1.4)
Catheter-peripheral blood and BOS culture	1 (1.4)

tant (36 patients lost, 65%), 12 patients (16.7%) were gentamicin sensitive (10 patients lost, 83%), 60 patients (83.3%) were gentamicin resistant (41 patients lost, 68%); and there was no statistically significant difference between antibiotic sensitivities and survival (Table 4).

Rectal swabs were taken from patients during hospitalization as of January 2018. According to the hospitalization data of 72 patients with CRKP growth, it was observed that no rectal swab was taken from 37 patients, while rectal swabs were taken from 35 patients. Rectal colonization was detected in 12 patients, six patients with rectal colonization survived, but six patients were lost.

During the CRKP growth, 38 patients (52.8%) had grade 1-2 mucositis, ten patients (13.9%) had grade 3-4 mucositis, and 24 patients (33.3%) had no mucositis. Among the patients with CRKP growth, 54 patients (75%) had no invasive pulmonary aspergillosis (IPA), while 12 patients (16.7%) presented probable and six patients (8.3%) presented proven IPA at that time of hospitalization. Ten patients received liposomal amphotericin B. Six patients received voriconazole, 36 received caspofungin, and 20 had no antifungal.

Among the patients with CRKP growth, 23 patients (31.9%) had steroids and beta-agonist, and 32 (44.4%) were followed up with ventilator support. In the follow-up, 48 patients (66.7%) died in the first 30 days after CRKP growth, and 51 (70.83%) died in 60 days. A total of 13 patients (18.05%) died due to CRKP bacteremia, 35 patients (48.61%) were lost due to disease progression and CRKP infection, while three patients (4.16%) were lost due to GVHD and disease progression.

Factors influencing survival were shown in Table 1. Given the factors influencing survival, the mortality rates of patients diagnosed with AML ($p = 0.003$), patients treated with remission induction treatment ($p = 0.002$), patients with the resistant disease ($p = 0.01$), patients who underwent allo- or autologous transplantation ($p = 0.019$), patients who developed septic shock ($p < 0.001$) and those conditioned to mechanical ventilation ($p < 0.001$) had significantly higher mortality rates. No significant relation was detected between mortality and sex, antibiotic sensitivity, allotransplantation, disease status at the time of transplantation, use of meropenem during growth, use of levofloxacin, neutrophil count during infection, stay in the intensive care unit, transfer from another centre, invasive procedure, empirical treatment, bacteremia during former neutropenic fever, colonization during former neutropenic fever, development of IPA, rectal colonization at the time of transplantation, GVHD or use of immunosuppressive treatment ($p > 0.05$).

DISCUSSION

The present study aimed to identify the clinical characteristics, laboratory findings, antimicrobial sensitivities, disease development and mortality risk fac-

Table 4. CRKP antibiotic sensitivity.

Antibiotics	Sensitive frequency n (%)	Medium sensitive frequency n (%)	Resistant frequency n (%)
Gentamicin	12 (16.7)	0	60 (83.3)
Amikacin	17 (23.6)	0	55 (76.4)
Colistin	44 (61.1)	0	28 (38.9)
Tigecycline	19 (26.38)	28 (38.9)	25 (34.72)

tors of patients that developed CRKP among those with haematological patients who received chemotherapy or underwent allogeneic or autologous stem cell transplantation. The prevalence of CRKP varies depending on geography. The prevalence in China is around 10%, while it rises to 60% in India.[19] The prevalence of CRKP is increasing, given the studies on patients with haematological malignancy. In a review of 30 studies from 21 countries to determine the global prevalence of carbapenem-resistant infections, carbapenem resistance was 9% on average, ranging between 2-53%. On the other hand, CRKP strains have been identified at a higher rate in countries such as Italy, Greece and Israel, and these regions have been identified as endemic areas.[20]

In this study, gram-negative bacteria growth was detected in 1,519 (8.31%) of 19,179 blood-urine-sputum cultures taken from patients hospitalized in the Haematology and Bone Marrow Transplantation Unit of our hospital for more than four years between 2015-2019. Among them, 302 cases (1.57%) were CRKP. In the retrospective 5-year data of a single centre, published by Kara *et al*.[21], bloodstream infection was 14.5%. Gram-negative bacteria accounted for 2% of the CRKP growth. In a study by Trecarichi *et al*.10 involving thirteen Haematology centres in Italy, CRKP accounted for 161 (57.9%) of the 278 cases of Klebsiella pneumoniae growth, isolated between January 2010 and June 2014, 117 (42.1%) of them was meropenem-sensitive *Klebsiella pneumoniae* (MSKP); 84 out of 161 (52.2%) meropenem-resistant patients and 17 out of 117 (14.5%) patients with MSKP growth died in 21 days ($p < 0.001$). Septic shock, acute respiratory failure, inadequate initial antimicrobial treatment and carbapenem resistance were associated with mortality as an independent risk factor. In the present study, during the follow-up, 48 patients (66.7%) died in the first 30 days after CRKP growth, and 51 patients (70.83%) died in 60 days. A total of 13 patients (18.05%) died due to CRKP bacteremia, 35 patients (48.61%) were lost due to disease progression and CRKP infection, while three patients (4.16%) were lost due to GVHD and disease progression. In haematology patients, risk factors for the development of CRKP infection were found to include age > 50 years, especially male sex, AML patients, relapse or refractory leukaemia, long-term hospitalized patients, long-term neutropenia, rectal CRKP colonization, prior CRKP bacteremia, patients with a central catheter or urinary catheterization.[9,22]

Given the factors influencing survival after CRKP infection in our study, the mortality rates of patients diagnosed with AML ($p = 0.003$), patients treated with remission induction treatment ($p = 0.002$), patients with the resistant disease ($p = 0.01$), patients who underwent allo- or autologous transplantation ($p = 0.019$), patients who developed septic shock ($p < 0.001$) and those conditioned to mechanical ventilation ($p < 0.001$) had significantly higher mortality rates. No significant relation was detected between mortality and sex, antibiotic sensitivity, allotransplantation, disease studies at the time of transplantation, use of meropenem during growth, use of levofloxacin, neutrophil count during infection, stay in the intensive care unit, transfer from another centre, invasive procedure, empirical treatment, bacteremia during former neutropenic fever, colonization during former neutropenic fever, development of IPA, rectal colonization at the time of transplantation, GVHD or use of immunosuppressive treatment ($p > 0.05$). The high mortality rates of patients included in the study were associated with the high number of patients with relapsed refractory haematological malignancy and those diagnosed with AML. In a study in which we examined the infections developed by 199 patients who underwent allogeneic stem cell transplantation during 219 transplants from November 2012 to July 2018, 9 patients presented CRKP. One patient had MSKP growth in the catheter and peripheral blood cultures, seven had CRKP, and four had MSKP growth in urine cultures. Two patients had CRKP, and one had MSKP growth in sputum cultures. Five patients were lost due to CRKP sepsis during the follow-up of patients with MRKP growth. Three of them presented resistance to colistin and tigecycline. Colistin and tigecycline resistance were detected in 20% of the patients.[23]

A comparison of the data of the two studies revealed that colistin and tigecycline resistance increased over time, which indicates that colistin resistance rises over the years and shows a high rate of dispersion.

In haematological patients, the CRKP colonization rate is 3.8% in Italy, while in India, it increases up to 21%. It was observed that 14% of the colonized patients developed bloodstream infections with the same bacteria.[24,25] In a study conducted by Micozzi *et al*.[26] on haematological patients at Sapienza University of Rome, CRKP rectal colonization was detected in 22

out of 373 patients from January 2014 to September 2014, 12 (64%) of which developed bacteremia; while rectal colonization was detected in 14 out of 131 initial patients, those patients were then isolated, rectal culture was started to be taken every week, and colonization rate continuously decreased in subsequent hospitalizations. Rectal colonization was detected in 5 of the 242 patients hospitalized after the rectal culture started to be taken routinely ($p = 0.001$). 14 (58%) of the 22 patients with rectal colonization developed bacteremia, and all had AML ($p = 0.02$). Bacteremia grew in the neutropenic period in 86% of the patients. Ten of the 14 patients who developed bacteremia died in the follow-up, all of whom had AML. Initial adequate antibiotic therapy resulted in the only independent factor to protect against death ($p = 0.02$). The researchers claimed that starting initial antibiotics for patients with rectal CRKP during NPF based on CRKP culture antibiogram colonization would reduce mortality.[26] The present study included patients admitted to the Haematology service between January 1, 2015, and August 31, 2019. Rectal swabs were taken from patients during hospitalization as of January 2018. According to the hospitalization data of 72 patients with CRKP growth, it was observed that no rectal swab was taken from 37 patients, while rectal swabs were taken from 35 patients. Rectal colonization was detected in 12 patients, six patients with rectal colonization survived, but six patients were lost. In a study by Micozzi *et al*.26, the colistin sensitivity was 50% (12/22), and tigecycline sensitivity was 27% (6/22), while all patients were gentamicin resistant (0/22). After the documentation of CRKP infection, patients are usually administered combination treatments. Tigecycline/amikacin/colistin, colistin/tigecycline/gentamicin and colistin/tigecycline/meropenem combinations are used. However, some studies reported a synergic effect against carbapenem-resistant bacteria in in vitro environments[27-29], while other studies did not show such a synergic effect.[30]

The late start of the combination treatment is one of the key factors affecting mortality.27,28 In the present study, 41 patients (56.94%) were given a combination of meropenem, amikacin, colistin and tigecycline; 15 patients (20.83%) received meropenem, colistin, tigecycline, and eight patients (11.1%) had meropenem, gentamicin, colistin and tigecycline. Other patients received single or double antibiotics (11.13%). Combination therapy with three or four antibiotics is recommended in CRKP infections. 88.87% of our patients used triple or quadruple combination antibiotic therapy as recommended. Treatment was directed according to the antibiotic susceptibility obtained as a result of the cultures. Therefore, our study found no statistical significance between antibiotic susceptibility and mortality.

CONCLUSIONS

Currently, carbapenems are used empirically as part of the first line of treatment during neutropenic fever in patients with haematological malignancy. The widespread use of carbapenems is one of the critical factors in the increase of carbapenem-resistant strains. Today, early detection of CRKP colonization in high-risk haematological patients (e.g. patients with AML who receive remission-induction treatment, patients with relapsed refractory AML, or patients to undergo allogeneic or autologous bone marrow transplantation), taking rectal culture as a routine procedure during hospitalization, and if the patient presents rectal colonization of CRKP or had CRKP bacteremia during prior hospitalizations, early initiation of treatment with combined antibiotics acting against CRKP during NPF (meropenem, aminoglycoside, colistin and tigecycline) would significantly reduce mortality.

Conflict of Interest

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İzmir Katip Çelebi University, İzmir, Turkey. (Decision number: 0259, date: May 2021).

Authors' Contribution

Study Conception, Supervision, Critical Review: SK, SÇ, GE; Study Design, Fundings: GE, SK,; Data Collection and/or Processing: SK, SÇ,; Analysis and/or Interpretation: SK, SÇ,; Materials: GE,; Literature Review, Writer: SK, SÇ.

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