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Original Article

Risk factors for bloodstream infections due to extended-spectrum β-lactamase producing *Enterobacteriaceae* in cancer patients

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Abstract

Introduction: Bloodstream infection (BSI) caused by *Enterobacteriaceae* is associated with mortality in cancer patients receiving chemotherapy. The aim of this study is to identify the risk factors and outcomes related to BSIs caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* in cancer patients.

Methodology: Hematology/oncology patients, who were diagnosed with BSIs caused by *Enterobacteriaceae* by positive blood cultures were evaluated retrospectively. Patients were divided into two groups by ESBL-positive and ESBL-negative *Enterobacteriaceae* bacteremia. Patients' demographic features, underlying conditions, comorbidity, neutrophil count, duration of neutropenia, antibiotic use in the previous three months before infection, mechanical ventilation, steroid use, central venous catheter implementation, total parenteral nutrition (TPN), hospitalization in the past three months, stay in intensive care unit, quinolone prophylaxis, and history of infection with ESBL-producing *Enterobactericeae* were evaluated. Risk factors related to BSIs caused by ESBL-producing *Enterobacteriaceae* and mortality were assessed.

Results: A total of 122 patients were evaluated retrospectively. Quinolone propyhlaxis, TPN, infection with Extended Spectrum Beta-Lactamase positive ESBL-P *Enterobacteriaceae* during the previous three months, treatment with piperasillin-tazobactam or carbapenems in the previous three months were found to be independent risk factors for ESBL-P BSIs. Longer duration of neutropenia before BSI and complication at the beginning of BSI were found to be independent risk factors for mortality related to infection.

Conclusions: ESBL-producing *Enterobacteriacea* should be treated with an appropriate antibiotic that is associated with better outcomes in hematology/oncology patients with BSIs. History of broad-spectrum antibiotic use and stay in hospital in the previous three months should be taken into consideration upon commencing antibiotic therapy.

Key words: Extended Spectrum Beta-Lactamase; *Enterobacteriaceae*; cancer; risk factors.

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Introduction

Bloodstream infection (BSI) is common in cancer patients receiving chemotherapy and it is associated with high morbidity and mortality rates [1]. These patients are immunocompromised due to chemotherapy, neutropenia, major surgery, malnutrition, transplantation or immunosuppressive treatment in addition to their underlying malignity [2].

An increase in the frequency of bacteremias caused by Gram-negative rods has been reported in many centers worldwide, with Gram-negative pathogens becoming either predominant or at least as frequent as Gram-positive pathogens [3]. This trend has been confirmed in a recent literature review and European surveillance study performed in 2011 in 39 hematology centers from 18 countries for the Fourth European Conference of Infections in Leukemia (ECIL-4) [4]. The high percentage of multidrug resistant microorganism is a world-wide problem. Extended-spectrum beta-lactamase (ESBL) production is the most common resistance type for *Enterobacteriaceae* [2,5,6]. The knowledge of risk factors for ESBL bloodstream infection (BSI) will contribute to identify patients who are at higher risk, in order to start empirical therapy with proper coverage against these microorganisms. There are few reports comparing the clinical, epidemiological and microbiological factors of ESBL-producing (ESBL-P) *Enterobacteriaceae* BSI in adult cancer

patients. This study was performed to evaluate the epidemiology of ESBL-P BSI in cancer patients and to assess the clinical impact of ESBLs on patients' outcome.

Methodology

The retrospective cohort study was conducted in a 550 beds teaching hospital. Hematology/oncology patients with culture positive BSIs with *E. coli* or *Klebsiella spp*, during a period of two years from January 2013 to December 2014, were included. Other *Enterobacteriaceae* strains were not included as they were very few in numbers. Patients' data and laboratory findings were collected by the electronic medical record database of the hospital retrospectively. Patients were divided into two groups, ESBL - positive (ESBL-P) and ESBL- negative (ESBL-N), according to ESBL production of the microorganism. If there was more than one positive blood culture, the first strain was included for each infection.

Demographic and infection-related data like age, gender, underlying disease, type of malignancy, chemotherapy regimen, comorbidities like diabetes mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), hematopoietic stem cell transplantation (HSCT), hospital unit in which the infection was detected, type of BSI (primary or secondary), neutrophil count and duration of neutropenia (< 500 neutrophils/mm^3) were recorded. Potential risk factors for infection with ESBL-P *Enterobacteriaceae* including history of hospitalisation and previous antibiotic use during the last three months, quinolone prophylaxis, duration of hospital stay before infection, stay in intensive care unit (ICU), history of mechanical ventilation support, total parenteral nutrition (TPN), steroid use, Granulocyte-colony stimulating factor (GCSF) use and central venous catheter use were recorded.

Outcomes of BSIs with ESBL-P *Enterobactericeae* were also evaluated. Appropriate initial antibiotic therapy was defined as a regimen that included at least one antibiotic that the isolated strain was susceptible to in vitro and started during the first 24 hours after the blood culture was obtained. If the first regimen was not appropriate, the day an adequate drug started was recorded. Presence of complications like septic shock, hypoxia and organ failure, length of stay in the hospital and mortality related with infection and overall mortality (infection and all other causes) in 30 days were also recorded. Mortality was defined as related to infection if it occurred in 14 days after positive blood culture and there was no other reason related to primary disease.

Identification of the bacteria and antimicrobial susceptibility testing were performed using conventional methods and a VITEK2 automated system (bioMérieux, Marcy l'Etoile, France) according to the recommendations of the Clinical and Laboratory Standard Institute (CLSI) [7].

Statistical Analysis

Statistical analyses were done using SPSS for Windows software, version 21.0. Chi-squared and Student's *t* tests were used for the univariate analysis of categorical and continuous variables of patient characteristics, respectively. Continuous variables with non-normal distribution were compared by using Mann-Whitney U test. Independent risk factors for ESBL-P bloodstream infections were evaluated by a multivariable model using logistic regression.

Results

122 patients with *E. coli* or *Klebsiella spp.* positive blood cultures were included in the study. The mean age ± standard deviation of the patients was 44.5 ± 15.55 and 89 (73%) of them were male. 112 patients (91.8%) had hematologic malignancy and 10 (8.2%) of them had solid tumors. 37 patients (30.3%) had hematopoietic stem cell transplantation (HSCT). 84 (68.8%) of the isolated microorganisms were *E. coli* and 38 (31.2%) of them were *Klebsiella spp*. 70 of the patients (57.4%) had BSI with ESBL–P microorganisms and 52 (42.61%) of them were ESBL-N. Demographic and clinical data of the patients are evaluated in Table 1.

We did not find a statistical significance between patients with ESBL-P and ESBL-N BSIs when we compared age, gender comorbidities, history of stay in ICU or mechanical ventilation support, central venous catheter use, neutrophil count and duration of neutropenia. There was no statistical significance in use of aminoglycosides and polymyxin E in the previous three months.

Quinolone prophylaxis (P: 0.018; OR: 2.46; CI: 1.15-5.28), total parenteral nutrition (P: 0,020; OR: 1,11; CI: 1,02-1,20), infection with ESBL-P *Enterobacteriaceae* during the previous three months (P: 0.026; OR: 4.66; CI: 0.98-22.02), treatment with piperasillin-tazobactam (P: 0,039; OR: 2.25; CI: 1.02-4.93) or carbapenems in the previous three months P: 0,016 OR: 3,28, CI: 1.53-7.06) were found to be independent risk factors for ESBL-P BSIs. Risk factors for ESBL-P BSIs are shown on Table 2.

Table 1. Demographic data and clinical features of patients with ESBL-positive or ESBL-negative bloodstream infection.

Features	Total n = 122	ESBL-P n = 70 (57.4%)	ESBL-N n = 52 (42.6%)	P
Mean age ± SD	44.5 ± 15.55	46.00 ± 14.78	42.48 ± 16.45	0.218
Male , n(%)	89 (73)	54 (77.1)	35 (67.3)	0.932
Diagnosis				
ALL, n(%)	31 (25.5)	21 (30.9)	10 (19.2)	0,210
AML, n(%)	44 (36.1)	22 (31.4)	22 (42.3)	0,255
NHL, n(%)	25 (20.5)	13 (18.6)	12 (23.1)	0,651
Other HM, n(%)	11 (9)	6 (8.6)	5 (9.6)	1,00
Solid tumor, n (%)	10 (8.2)	8 (11.4)	2 (3.8)	0,187
Chemotherapy regimen				
HSCT (non myeloablative), n (%)	4 (3.2)	2 (1.6)	2 (1.6)	1,00
HSCT (myeloablative), n (%)	31 (25.4)	16 (13.1)	15 (12.2)	0,530
Acute leukemia induction, n (%)	38 (31.1)	25 (20.4)	13 (10.6)	0,124
Consolidation / intensification, n (%)	16 (13.1)	11 (9.0)	5 (4.0)	0,180
Acute leukemia other	5 (4.0)	3 (2.4)	2 (1.6)	1,00
Lymphoma primer	7 (5.7)	5 (4.0)	2 (1.6)	0,458
Lymphoma salvage	7 (5.7)	4 (3.2)	3 (2.4)	1,00
Others	14 (11.4)	4 (3.2)	10 (8.1)	0,046

ESBL-P: extended spectrum beta lactamase positive, ESBL-N: extended spectrum beta lactamase negative, p value ≤ 0.05 is significant, SD: standard deviation, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, NHL: Non Hodgkin Lymphoma, HM: Hematologic Malignancy, HSCT: Hematopoietic Stem Cell Transplantation.

Table 2. Risk factors for EBL-P and ESBL-N bloodstream infections.

Variable	Univariate analysis			Multivariate Logistic regression
	ESBL-N n = 52	ESBL-P n = 70	P value	OR (95% CI)
Mean age ± SD	42.48 ± 16.45	46.00 ± 14.78	0.218	
Male, n (%)	35 (67.3)	54 (77.1)	0.932	
Type of infection			0.141	
Primer bacteremia, n (%)	26 (50)	44 (62.9)		
Catheter related bacteremia, n (%)	20 (38.5)	23 (32.9)		
Others, n (%)	6 (11.5)	3 (4.3)		
Neutrophil count,mm^3 (IQR)	30 (10-95)	30 (10-60)	0.230	
Duration of neutropenia before infection, days (IQR)	6.5 (3.25-12)	7.5 (4.75-13)	0.274	
Quinolone prophylaxis, n (%)	15 (28.8)	35 (50)	0.018	OR:2.46 (1.15-5.28)
Specific antibiotics previous 90 days				
Piperacillin tazobactam, n (%)	15	28	0.039	OR:2.25 (1.02-4.93)
Carbapenem, n (%)	6 (11.5)	22 (31.4)	0.016	OR:3.28 (1.53-7.06)
Polymyxin E, n (%)	3 (5.8)	2 (2.9)	0.426	
Aminoglycoside, n (%)	0	2 (2.8)	0.674	
Daptomycin, n (%)	3 (5.8)	10 (14.2)	0.120	
Glycopeptide, n (%)	8 (15.3)	14 (20)	0.896	
Hospital stay during the previous 3 months, n(%)	29 (55.8)	46 (65.7)	0.254	
Gram-negative infection during the previous 3 months, n (%)	2 (3.8)	11 (15.7)	0.026	OR:4.66 (0.98-22.02)
Comorbidity, n (%)				
DM, n (%)	6 (11.5)	8 (11.1)	0.356	
COPD	3 (5.8)	2 (2.9)	0.426	
Central venous catheter, n (%)	31 (59.6)	47 (67.1)	0.436	
History of ICU stay, n (%)	0	1 (1.4)	0.574	
History of MV, n (%)	0	1 (1.4)	0.1	
TPN, n (%)	0	7 (10)	0.020	OR: 1.11 (1.02-1.20)
GCSF, n (%)	34 (65.4)	46 (65.7)	0.970	
Steroid, n (%)	5 (9.6)	13 (18.6)	0.203	
Length of stay before infection, days (IQR)	10 (6-16)	13.5 (10-18)	0.231	

OR: odds ratio, CI: Confidence interval, IQR: Interquartile Range, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, ICU: Intensive Care Unit, MV: Mechanical Ventilation, TPN: Total Parenteral Nutrition, GCSF: Granulocyte Colony Stimulating Factor.

Table 3. Outcomes of ESBL-P and ESBL-N bloodstream infections.

Variable	Univariate analysis			Multivariate logistic regression
	ESBL-N n = 52	ESBL-P N = 70	P value	OR (95% CI)
Total Length of Stay, days(IQR)	25.5 (18-37)	28 (22-42.25)	0.105	
Complications (hypoxia, septic shock etc.) n (%)	6 (11.5)	24 (34.2)	0.046	OR: 2.22 (0.996-4.961)
Mortality related to infection Days (%)	4 (7.7)	19 (27.1)	0.009	OR: 4.47 (1.41-14.09)
30-day mortality Days (%)	8 (15.4)	23 (32.9)	0.025	OR:2.69 (1.09-6.64)

ESBL-P: extended spectrum beta lactamase positive, ESBL-N: extended spectrum beta lactamase negative, p value ≤ 0.05 is significant, OR: odds ratio, CI: Confidence interval, IQR: Interquartile Range.

Quinolone prophylaxis was also significantly related to quinolone resistance (P: 0,0005; OR: 20,455, CI: 7,14-58,52). Steroid use and GSCF use were higher in ESBL-P patients but it was not statistically significant. Although the length of hospital stay before infection and total length of hospital stay were higher in patients with ESBL-P BSIs, there was no statistical significance.

We assessed the outcomes of ESBL-P and ESBL-N BSIs, too. The length of hospital stay was higher in patients with ESBL-P BSI but it was not statistically significant (P: 0.105). Complications like septic shock and organ failure (P: 0.046 CI: 0.996-4.961 OR: 2.22), all-cause 30 days mortality (P: 0.034 CI: 1.13-6.95 OR: 2.69) and mortality related to infection (P: 0.025 CI: 1.41 -14.68 OR: 2.69) were significantly higher in patients with ESBL-P BSIs. Outcomes of patients with ESBL-P and ESBL-N BSIs are shown in Table 3.

The all-cause mortality was higher in patients that were treated with inappropriate antibiotics in the beginning. (P: 0.03, r: -267)

Univariate analysis identified BSI with ESBL-P microorganism in the previous three months, neutropenia, longer duration of neutropenia before BSI, inappropriate treatment at the beginning, delay at starting appropriate treatment and complication at the beginning of BSI as risk factors for mortality related to infection. Multivariate logistic regression identified longer duration of neutropenia before BSI and complication at the beginning of BSI as independent risk factors for mortality related to infection. Risk factors for mortality related to infection are shown in Table 4.

Discussion

Infections with resistant Gram-negative microorganisms in cancer patients are relevant because of an inherent risk of treatment failure of the infection, which contributes to morbidity and mortality. In this study, patients infected with *Enterobacteriaceae spp.* were evaluated and ESBL positivity was found to correlate with higher mortality.

Early diagnosis and treatment of ESBL-positive patients were found to decreasemortality. In this study, we found that infection with ESBL-positive Gram-negative bacteria in the past three months, history of quinolone, piperasilin- tazobactam or carbapenem treatment in the past three months and total parenteral nutrition were independent risk factors for ESBL positivity in cancer patients.

Table 4. Risk factors for mortality related to infection.

Variable	Univariate analysis			Multivariate logistic regression
	Survivors	Non-survivors	P value	OR (95% CI)
Mean age ± SD	43.38 ± 15.66	49.30 ± 14.39	0.089	
Male	73 (73.7%)	16 (69.6%)	0.686	
ESBL-P n (%)	51 51.5 (%)	19 (82.6%)	0.013	
Neutropenia, n (%)	30 (30.3%)	14 60.9 (%)	0.012	
Duration of neutropenia before infection, days (IQR)	6 (4-11)	11 (5-29)	0.013	1.1 (1.035-1.168)
Length of stay before infection, days (IQR)	12 (8-16)	14 (9-25)	0.3	
Inappropriate treatment at the beginning, n (%)	30 (30.3%)	14 (60.8%)	0.012	
Delay at starting appropriate treatment, day (min-max)	1.26 ± 0.88	2.5 ± 2.06	0.019	
Complications (hypoxia, septic shock etc.), n(%)	79 (79.8%) 20 (20.2%)	3 (13%) 20 (87%)	0.000	39.634 (8.010-196.113)
Central venous catheter, n(%)	61 (61.6%)	17 (73.9%)	0.33	

p value ≤ 0.05 is significant, OR: odds ratio, CI: Confidence interval, IQR: Interquartile Range.

Prevention, early diagnosis and prompt treatment of ESBL-positive Gram-negative infections are vital in immunocompromised patients with underlying malignity. The prevalence of ESBL-positive Gram-negative infections is increasing among community-acquired as well as health care-associated infections [8].

The use of immunosuppressive agents and corticosteroids is associated with the development of ESBL-positive Gram-negative infections. A study in mice showed that the use of immunosuppressive drugs causes bacterial translocation from the intestinal tract and bacteremia. ESBL-positive microorganisms lead to more frequent infections in this population [9,10]. ESBL-positive microorganisms have been shown to be located in the lower intestinal tract, and this region is usually the source for these infections [11].

In this study, 122 patients with hematologic and solid organ malignancies were evaluated. All of the patients were receiving immunosuppressive treatment. Fluoroquinolone prophylaxis is used to prevent infections in patients with profound prolonged neutropenia. Fluoroquinolone prophylaxis was used during the neutropenic period after allogeneic HSCT until engraftment for a short period in our hospital. Breakthrough infections with fluoroquinolone resistant Gram-negative bacteria are reported in recent studies [12,13]. Fluoroquinolone prophylaxis has a potential role in infection with MRSA and *Clostridium difficile* and ESBL-producing *Enterobacteriaceae* as well as fluoroquinolone-resistant strains [6,14,15].

However, there are some studies showing that fluoroquinolone prophylaxis does not increase the risk of infection with resistant microorganisms. Satlin *et al.* reported that levofloxacin prophylaxis did not increase MDR Gram-negative bacterial infection in 475 multiple myeloma patients undergoing autologous HSCT [16]. We identified fluoroquinolone prophylaxis as a risk factor for ESBL-P bloodstream infection as well as for quinolone resistance.

Antibiotic exposure during the last three months has been reported as a risk factor for infections with resistant Gram-negative microorganisms [17]. We found that using piperacillin-tazobactam, quinolones and carbapenems during the previous three months is a risk factor for ESBL-P infections. There was no statistical significance in use of aminoglycosides and polymxyn E, which may be due to the low number of patients treated with these drugs before BSI in our study. There was no usage of cephalosporins during the last three months so we could not demonstrate the impact of these drugs on ESBL–P bacteremia.

In a study involving 118 cancer patients, longer duration of hospitalization and cephalosporin, macrolide, quinolone and aminoglycoside treatment before infection were reported as independent risk factors for ESBL-positive BSIs. There was no significant difference in mortality in patients with ESBL-positive and negative BSIs in this study [18].

Risk factors for colonization / infection with ESBL-producing microorganisms were assessed in a meta-analysis including 14 studies (746 cases and 1257 controls). Parenteral nutrition, mechanical ventilation, use of central venous catheter, previous ampicillin, gentamicin and cephalosporin treatment were found to increase colonization / infection with ESBL-positive microorganisms [19].

Piperacillin/tazobactam is a good choice for the treatment of hospital-acquired infections, caused by *Pseudomonas spp*. and ESBL-positive microorganisms [20]. It is thought that it can be used as an alternative to carbapenems to treat infections with resistant Gram-negative bacteria [21,22]. Although piperacillin/tazobactam is considered to be a good option for treatinginfections with Gram-negative microorganisms, there are some studies showing that it promotes accumulation of ESBL-positive Enterobacteriaceae in the intestinal flora of patients [23,24]. Piperasilin-tazobactam treatment in the previous three months was identified as an independent risk factor for BSI with ESBL-P in our study.

Prior colonization or infection by resistant organisms is one of the most important risk factors for developing an infection with ESBL-P microorganisms [18,25,26]. We do not perform surveillance cultures for screening multidrug-resistant Gram-negative bacteria, therefore we could not assess the impact of colonization with these microorganisms in our patients. However, we found that infection with ESBL-P *Enterobacteriaceae* during previous three months is an individual risk factor for ESBL-P bacteremia. Infection and colonization with resistant microorganisms increase mortality and morbidity. To prevent this, it is necessary to avoid inappropriate antibiotic treatment [18].

Prolonged hospital stay and/or repeated hospitalizations have also been found to be risk factors for infection with resistant bacteria [14,27]. Duration of hospitalization was reported as an independent risk factor for infection with multidrug-resistant ESBL-P *E. coli* and *K. pneumoniae* BSIs in one study from Turkey. [28]. Although the number of patients staying in hospital during previous three months was higher and the duration of hospital stay prior to BSI was longer in

the ESBL-P group than in the ESBL-N group, this was not reflected in a statistically significant difference in our study.

Total parenteral nutrition (TPN) is a risk factor for bacteremia and candidemia [16,29,30]. We identified TPN as an independent risk factor for ESBL-P BSIs. Univariate analysis identified receiving TPN in the previous 30 days as a potential risk factor for acquiring ESBL-P *Enterobacteriaceae* among the paediatric population in one study [31]. There is a need for more studies about the role of TPN in infections with resistant Gram-negative bacteria.

Infection with multidrug-resistant Gram-negative bacteria was reported to be associated with a high mortality in cancer patients in the literature [32-36]. Matsuma *et al.* found that the 30-day mortality was higher in patients with ESBL-positive BSIs than the ones with ESBL-negative BSIs [37]. Conversely, ESBL positivity did not have a negative effect on mortality in some studies. Namikawa *et al.* reported that there was no significant difference in mortality according to age, underlying diseases, CRP level, white blood cell numbers of the patients and ESBL positivity of the microorganism [10]. Although univariate analysis showed that the mortality rate was higher in ESBL-P group, we did not identifiy ESBL-P BSI as an independent risk factor for mortality.

Early initiation of treatment with appropriate antibiotics in bacteremic patients prevents sepsis and reduces mortality.

Metan *et al.* assessed the relationship between multidrug-resistant Gram-negative bacteremia and mortality and found that inappropriate antibiotic treatment was higher in patients who did not survive seven days after bacteremia onset. However, they could not demonstrate a significance of this finding by multivariate analysis [38]. In our study, mortality related to infection was higher in the patients that were treated with inappropriate antibiotics in the beginning, but inappropriate therapy was not an independent risk factor for mortality related to infection when analysed by multivariate logistic regression. In this study we defined infection-related mortality as mortality occurring within 14 days after the first positive blood culture.

30 (30.3 %) out of 99 survivors and 14 (60.9%) of the patients who did not survive had been neutropenic when they had BSI. Duration of neutropenia was higher in non-survivors. Higher duration of neutropenia was found to be an independent risk factor for mortality related to infection in our study. Complications like hypoxy, septic shock etc. were more common in patients who did not survive, which is in accordance with the literature.

Our study has some limitations. We only evaluated patients from one center. Patients‘profiles may vary in other hospitals. The design of the study is retrospective, therefore we could not take all possible risk factors like travel history or colonisation with ESBL-P bacteria before the infection and outcomes related to ESBL-P BSIs into consideration.

Conclusions

ESBL-P *Enterobacteriaceae* should be kept in mind in BSIs of hematology/oncology patients with previous broad spectrum antibiotic use and stay in hospital in previous 3 months, as starting appropriate antibiotic treatment is life-saving in these patients. Broad-spectrum antibiotics should promptly be given to patients with prolonged neutropenia and unstable clinical conditions like hypoxy, septic shock or organ failure.

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