



Risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae infection causing septic shock in cancer patients with chemotherapy-induced febrile neutropenia

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Abstract

Patients with chemotherapy-induced febrile neutropenia (FN) are vulnerable to extended-spectrum b-lactamase-producing Enterobacteriaceae (ESBL-PE) infection. Early identification of patients suspected to have ESBL-PE infection for empirical carbapenem administration is crucial; nevertheless, risk factors for ESBL-PE causing septic shock remain unclear. We identify factors to predict ESBL-PE in septic shock patients with chemotherapy-induced FN. In this observational, prospectively collected registry-based study, consecutive adult chemotherapy-induced FN patients with septic shock who were admitted to the emergency department between June 2012 and June 2018 were enrolled. Clinical and laboratory data extracted from the septic shock registry were assessed to identify risk factors for ESBL-PE. Of 179 chemotherapy-induced FN septic shock patients, ESBL-PE is isolated in 23 (12.8%). ESBL-PE infection is frequently seen in patients with hepatobiliary cancer (17.4% vs. 4.5%, $P=0.037$), leukemia (13.0% vs. 2.6%, $P=0.046$), and those with profound neutropenia (defined as absolute neutrophil count < 100) (73.9% vs. 43.6%, $P=0.007$) in contrast to those with lung cancer (0% vs. 14.7%, $P=0.048$) and other solid cancer (0% vs. 19.2%, $P=0.016$). Multivariate logistic regression reveals that profound neutropenia (adjusted OR 3.67; 95% CI 1.372–9.799; $P=0.010$) is an independent risk factor for ESBL-PE infection after adjusting age, the presence of solid tumor, and the parameters of sepsis severity scores. ESBL-PE is rare (12.9%) in chemotherapy-induced FN patients with septic shock. Early empirical carbapenem therapy might be considered in chemotherapy-induced FN patients with profound neutropenia.

Keywords Chemotherapy-induced febrile neutropenia · Septic shock · Beta-lactam resistance · Enterobacteriaceae infections · Multidrug resistance

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Introduction

Cancer patients are vulnerable to infection, because they are easily immunocompromised due to chemotherapeutic agents, neutropenia, malnutrition, transplantation, or immunosuppressant use. Neutropenia is the most common

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unfavorable consequence of chemotherapeutic agents, and infection can rapidly progress in neutropenic cancer patients. Therefore, the administration of prompt empiric antimicrobial therapy is crucial in patients with febrile neutropenia (FN), and current guidelines recommend monotherapy with an antipseudomonal β -lactam agent for high-risk patients who require hospitalization (level of evidence I, grade of recommendation A) [1].

The epidemiology of microbiological pathogens during neutropenia in cancer patients has changed in recent decades with the spread of extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-PE) from hospital environments to the community [2, 3]. ESBL-PE are generally resistant to most β -lactam antibiotics; carbapenems are considered the drugs of choice for the empiric treatment of serious ESBL-PE infections. However, their consequent increased use has likely contributed to the spread of carbapenem resistance [4, 5]. Thus, clinicians responsible for infection diagnosis and management should identify patients with chemotherapy-induced FN possibly infected with ESBL-PE, and immediately administer appropriate empirical therapy, especially those patients with septic shock. Although several reports have suggested that risk factors such as recent antimicrobial use [6–9], history of ESBL infection [10], and chronic indwelling vascular device use [10, 11] predict the presence of ESBL pathogens, to our knowledge, no previous study has focused on the factors associated with septic shock in cancer patients with chemotherapy-induced FN. The objective of this study is to identify risk factors suggestive of ESBL-PE infection in septic shock patients with chemotherapy-induced FN to guide appropriate antibiotic therapy.

Methods

Study design

This single-center, observational, prospectively collected registry-based study was performed at an ED with an annual census of about 110,000 visits at a tertiary care university-affiliated hospital in Seoul, Korea. Adult (≥ 18 years) patients with septic shock admitted to the ED were enrolled, with their data prospectively collected in the septic shock registry of our hospital from June 2012. The patients were enrolled in the septic shock registry when they showed evidence of refractory hypotension or hypoperfusion and suspected or confirmed infection [12]. Refractory hypotension is defined as persistent hypotension (systolic blood pressure < 90 mmHg, a mean arterial pressure < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg) after 20–30 mL/kg or more intravenous fluid challenge, or requiring vasopressors to maintain a systolic blood pressure ≥ 90 mmHg, or

a mean arterial pressure ≥ 70 mmHg [12]. Hypoperfusion is defined as serum lactate levels ≥ 4 mmol/L [13]. Our septic shock registry did not include patients who refused intensive care treatment, and who signed a “Do Not Attempt Resuscitation” order, were directly transferred from the ED to other hospitals, or refused to enroll in the registry. The institutional review board of our hospital approved the registry and informed consent was obtained before data collection.

Patients' selection

In this study, data from patients with chemotherapy-induced FN who were admitted to the ED between June 1, 2012, and December 31, 2017, were extracted from the septic shock registry. Patients who met the following criteria were included in this study: those who received chemotherapy prior to the episode; documented fever, defined as an oral temperature > 38.3 °C or two consecutive readings > 38.0 °C in 2 h; and an absolute neutrophil count (ANC) of 500/ μ L or expected to fall below 500/ μ L within 48–72 h [1]. Patients were categorized into ESBL-PE infection or non-ESBL-PE infection groups. ESBL-PE infection was defined as the isolation of ESBL-PE from at least one positive blood culture or urine culture.

Management and data collection

All patients were treated in accordance with current guidelines and bundles of survival sepsis campaign, such as the administration of crystalloid, obtaining blood cultures prior to the administration of antibiotics, and administration of broad-spectrum antibiotics and vasopressors [12, 14, 15]. In our institution, three sets of blood cultures are obtained from three different sites from all patients before the use of antibiotics; for patients with central venous catheter, a set of blood cultures is collected through an indwelling central venous catheter. Empirical broad-spectrum antibiotics including piperacillin/tazobactam or cefepime as monotherapy, or ceftazidime and cefazolin in combination are administered immediately after blood cultures, and further antibiotic treatments after admission are adjusted according to the results of blood cultures or the patient's status. Granulocyte colony-stimulating factor (G-CSF) is administered after the initiation of antibiotics at a dose of 5 μ g/kg per day until the ANC reached 500/ μ L [16].

Microbiological ESBL is diagnosed according to the Clinical and Laboratory Standards Institute M100 [17]. These are performed using MicroScan NC72 panels (Beckman Coulter, Inc., Brea, CA, USA), which measure the minimum inhibitory concentration around both cefotaxime and ceftazidime disks with or without clavulanate for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*.

The demographic characteristics of the patients, including age, gender, and primary site of cancer, comorbidities, focus of infection, initial laboratory findings, sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation (APACHE) II scores, 28-day mortality, and in-hospital mortality were retrieved from the septic shock registry. Additional data were also collected for this study, including Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, the use of antibiotics in the previous 6 months and hospitalization in the previous 3 months, healthcare-associated infection, previous infection related to ESBL-PE, the presence of indwelling catheters or other devices, previous FN event, and date of death. Healthcare-associated infection is defined as an infection in patients with any of the following risk factors: attendance at a hospital or hemodialysis clinic in the previous 30 days, or residence in a nursing home or long-term care facility [18, 19]. The indwelling catheters or other devices included central venous catheters, chemoport, peripherally inserted central catheter, foley catheter, pigtail catheter, and percutaneous nephrostomy.

Statistical analysis

Continuous variables are expressed as mean with standard deviation or median with interquartile ranges (IQRs) according to their distribution by Kolmogorov–Smirnov tests. Categorical data are presented as absolute numbers and percentages. Differences between mean and medians were analyzed using the Student's *t* test and Mann–Whitney *U* tests, respectively. Differences between categorical variables were analyzed using Chi-square or Fisher's exact tests, as appropriate. A stepwise backward logistic regression analysis was used to identify whether profound neutropenia was the independent risk factors for ESBL infection after adjusting age, the presence of solid tumor, and the parameters of sepsis severity scores. The results were summarized by estimating the odds ratios (ORs) and 95% confidence intervals (CIs). Variables were tested for goodness-of-fit using the Hosmer–Lemeshow method. A two-tailed *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Between June 2012 and June 2018, 2038 patients were enrolled in the septic shock registry and 179 patients were diagnosed with chemotherapy-induced FN (Fig. 1). These patients were categorized into ESBL-PE infection (*n* = 23, 12.8%) and non-ESBL-PE infection (*n* = 156, 87.2%) groups.

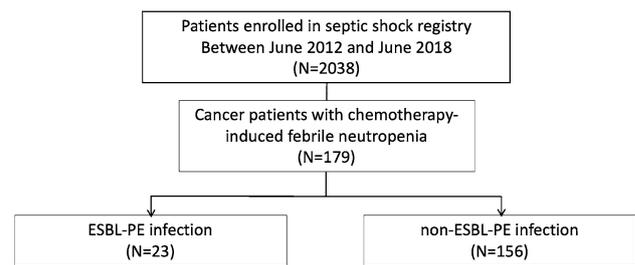


Fig. 1 Flow diagram of the study patients. *ESBL-PE* Extended-spectrum b-lactamase-producing Enterobacteriaceae

The demographic and clinical characteristics of patients are summarized in Table 1. ESBL-PE infection is more frequently documented in patients with hepatobiliary malignancy (17.4% vs. 4.5%, *P* = 0.037) and leukemia (13.0% vs. 2.6%, *P* = 0.046) in contrast to those with lung cancer (0% vs. 14.7%, *P* = 0.048) and other solid cancers (0% vs. 19.2%, *P* = 0.016). Our patients have a median SOFA score of 8.0 (IQR, 6.0–11.0) and a median APACHE II score of 22.0 (IQR, 17.0–29.0) and the severity scores do not differ between the two groups. The laboratory findings do not differ between the two groups except for white blood cell count (median, 300/μL vs. 600/μL, *P* = 0.022), which are lower in the ESBL-PE group. Profound neutropenia, defined as ANC < 100/μL, is more frequent in ESBL-PE group (73.9% vs. 43.6%, *P* = 0.007). *Escherichia coli* is the most prevalent bacteria isolated from blood or urine cultures in both ESBL-PE (19/23, 82.6%) and non-ESBL-PE (28/156, 17.9%) groups (Supplement Table 1).

In univariate analysis, only profound neutropenia (OR, 3.29; 95% CI, 1.218–8.898; *P* = 0.019) shows a significant association with ESBL-PE infection (Table 2). Profound neutropenia (adjusted OR, 3.67; 95% CI, 1.372–9.799; *P* = 0.010) is an independent risk factor for ESBL-PE infection after adjusting age, the presence of solid tumor, and the parameters of sepsis severity scores. The presence of profound neutropenia in chemotherapy-induced FN patients with septic shock predicts ESBL-PE infection with a sensitivity of 73.9%, a specificity of 56.4%, a positive predictive value of 20.0, and a negative predictive value of 93.6% (Table 3).

Discussion

This study shows that ESBL-PE is a rare pathogen among chemotherapy-induced FN patients with septic shock (12.9%). Patients with profound neutropenia (adjusted OR, 3.67; 95% CI, 1.372–9.799; *P* = 0.010) are more likely to develop FN septic shock caused by ESBL-PE. This result shows that carbapenems might be considered

Table 1 Clinical characteristics of the study patients

	Total (n = 179)	ESBL-PE infection group (n = 23)	Non-ESBL-PE infection group (n = 156)	P value
Age, years	63.5 (9.82)	62.0 (12.15)	63.7 (9.45)	0.513
Male	100 (55.9)	13 (56.5)	87 (55.8)	0.946
ECOG PS				0.373
0,1	101 (56.4)	11 (47.8)	90 (57.7)	
2,3,4	78 (43.6)	12 (52.2)	66 (42.3)	
Comorbidities				
Hypertension	51 (28.5)	3 (13.0)	48 (30.8)	0.079
Diabetes mellitus	21 (11.7)	2 (8.7)	19 (12.2)	>0.999
Chronic renal failure	8 (4.5)	1 (4.3)	7 (4.5)	>0.999
Liver cirrhosis	10 (5.6)	2 (8.7)	8 (5.1)	0.619
Malignancy				0.441
Solid	136 (76.0)	16 (69.6)	120 (76.9)	
Hematologic	43 (24.0)	7 (30.4)	36 (23.1)	
Type of malignancy				
Solid				
Gynecologic	42 (23.5)	8 (34.8)	34 (21.8)	0.170
Lung	23 (12.8)	0 (0)	23 (14.7)	0.048
Breast	16 (8.9)	1 (4.3)	15 (9.6)	0.698
Genitourinary	14 (7.8)	3 (13.0)	11 (7.1)	0.395
Hepatobiliary	11 (6.1)	4 (17.4)	7 (4.5)	0.037
Others	30 (16.8)	0 (0)	29 (19.2)	0.016
Hematologic				
Lymphoma	29 (16.2)	3 (13.0)	26 (16.7)	>0.999
Leukemia	7 (3.9)	3 (13.0)	4 (2.6)	0.046
Others	8 (4.5)	1 (4.3)	7 (4.5)	>0.999
No previous FN event	140 (78.2)	19 (82.6)	121 (77.6)	0.584
Duration of neutropenia, days	2.0 (2.0–4.0)	3.0 (2.0–6.0)	2.0 (2.0–4.0)	0.071
SOFA	8.0 (6.0–11.0)	8.0 (6.0–12.0)	8.0 (6.0–11.0)	0.849
APACHE II	22.0 (17.0–29.0)	24.0 (17.0–28.0)	22.0 (17.0–29.0)	0.637
Focus of infection				0.384
Respiratory	65 (36.3)	5 (21.7)	60 (38.5)	
Gastrointestinal	31 (17.3)	4 (17.4)	27 (17.3)	
Hepatobiliary	10 (6.1)	1 (4.3)	9 (5.8)	
Others	21 (11.7)	5 (21.7)	16 (10.3)	
Unknown	52 (29.1)	8 (34.8)	44 (28.2)	
Presence of indwelling catheters or other devices	41 (22.9)	4 (17.4)	37 (23.7)	0.500
Previous intravenous antibiotic use				
Within 30 days	33 (18.4)	6 (26.1)	27 (17.3)	0.385
Within 3 months	82 (45.8)	11 (47.8)	71 (45.5)	0.835
Within 6 months	108 (60.3)	16 (69.6)	92 (59.0)	0.332
Previous episode of ESBL-PE bacteremia				
Within 6 months	2 (1.1)	0 (0)	2 (1.3)	>0.999
Any event	6 (3.4)	2 (8.7)	4 (2.6)	0.172
Recent hospitalization (<3 months)	130 (72.6)	16 (69.6)	114 (73.1)	0.724
Healthcare-associated infection	93 (52.0)	13 (56.5)	80 (51.3)	0.639
Laboratory findings				
WBC/ μ L	500 (300–1100)	300 (200–800)	600 (300–1100)	0.022
ANC/ μ L	120 (20–350)	40 (20–160)	135 (20–368)	0.056
Profound neutropenia (ANC < 100)	85 (47.5)	17 (73.9)	68 (43.6)	0.007

Table 1 (continued)

	Total (<i>n</i> = 179)	ESBL-PE infection group (<i>n</i> = 23)	Non-ESBL-PE infection group (<i>n</i> = 156)	<i>P</i> value
Lactic acid, mmol/L	3.1 (1.9–4.8)	3.1 (2.3–4.9)	3.1 (1.8–4.8)	0.343
CRP, mg/dL	15.2 (6.5–21.8)	18.1 (4.5–21.8)	15.2 (6.6–21.7)	0.955
Procalcitonin, ng/mL ^a	10.8 (2.2–45.9)	6.8 (1.9–59.8)	10.9 (2.2–43.5)	0.596
Positive blood culture	87 (48.6)	21 (91.3)	66 (42.3)	<0.001
28-day mortality	51 (28.5)	8 (34.8)	43 (27.6)	0.474
In-hospital mortality	46 (25.7)	9 (39.1)	37 (23.7)	0.114

Data are presented as *n* (%) or median with interquartile ranges

^aProcalcitonin was not measured for 6 patients in non-ESBL-PE group

ESBL-PE extended-spectrum beta-lactamases-producing Enterobacteriaceae, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *FN* febrile neutropenia, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation, *WBC* white blood cell, *ANC* absolute neutrophil count, *CRP* C-reactive protein

Table 2 Univariate and multivariate analyses for ESBL-PE infections in the study patients

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i> value	Adjusted OR	95% CI	<i>P</i> value
Age (years)	0.98	0.941–1.026	0.423			
Presence of solid tumor	0.69	0.262–1.796	0.443			
SOFA	1.00	0.882–1.123	0.937			
APACHE II	1.00	0.957–1.053	0.865			
Profound neutropenia	3.29	1.218–8.898	0.019	3.67	1.372–9.799	0.010

ESBL-PE extended-spectrum beta-lactamases-producing Enterobacteriaceae, *OR* odds ratio, *CI* confidence interval, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation

Table 3 Performance parameters for the predictors of ESBL-PE infections in the study patients

Variables	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Presence of solid cancer	69.57 (47.08–86.79)	23.08 (16.72–30.49)	11.76 (9.12–15.04)	83.72 (72.24–91.04)
Profound neutropenia	73.91 (51.59–89.77)	56.41 (48.25–64.32)	20.00 (15.61–25.26)	93.62 (87.91–96.73)
Profound neutropenia in patients with solid cancer	43.48 (23.19–65.51)	69.23 (61.35–76.36)	17.24 (11.00–25.99)	89.26 (85.12–92.35)

ESBL-PE extended-spectrum beta-lactamases-producing Enterobacteriaceae, *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval

for the treatment of septic shock patients with profound neutropenia.

In the present study, the prevalence of ESBL-PE infection is 12.9% (23/179) among FN septic shock patients. Despite the regional and temporal differences and heterogeneous populations according to underlying malignancies, ESBL-PE is the causative pathogen in 11% of bloodstream infections in cancer patients [20]. To our knowledge, there has been only one cohort study of febrile neutropenic patients with severe sepsis and septic shock [21], which reported microbiologically documented infections in 55.5% of cases (237/428) and that

Enterobacteriaceae are one of the most prevalent pathogens (85/428, 19.9%) [21], which is consistent with our results.

Among FN septic shock patients, the frequency of ESBL-PE infection is significantly different in patients of underlying lung, hepatobiliary, other solid cancer, and leukemia despite its small proportion in our cohort. Although there is little information on bloodstream infection in patients with solid tumors, biliary tract obstruction, a common complication in hepatobiliary cancer patients, is recurrently complicated with ascending cholangitis and bacteremia [22]. Royo-Cebrecos et al. report that the risk of multidrug-resistant

organisms is particularly increased after the second episodes of cholangitis in patients with solid tumors [23]. In addition, invasive procedures such as biliary prosthesis and the presence of biliary drainage catheter, commonly performed for those with hepatobiliary cancer, are well-known risk factors for the development of multidrug-resistant organisms [24, 25].

Immunosuppressed patients with malignancy have increased risks of sepsis and septic shock, which are inversely proportional to the neutrophil count [26, 27]. Almost half of our cohort (47.5%) show a profound neutropenia upon ED presentation, which is the only independent risk factor for ESBL-PE infection (adjusted OR, 3.67; 95% CI, 1.372–9.799; $P=0.010$). Reduced ANC in cancer patients is reportedly a risk factor for bloodstream infection due to multidrug-resistant Gram-negative bacteria [28, 29]. In our study, profound neutropenic patients are at particularly high risk for ESBL-PE infections, with a sensitivity of 73.9% and a negative predictive value of 89.3%.

Recent antibiotic therapy [30], admission to long-term care facilities [28], and the presence of indwelling central venous catheters or other devices have been reported to be the major risk factors for ESBL-PE bacteremia [25, 31]. In contrast to these previous studies, we do not observe an association between ESBL-PE infection and risk factors including the presence of indwelling central venous catheters or other devices, recent antibiotic therapy, recent hospitalization, and healthcare-associated infection in our cohort. These differences might be due to differences in patient populations or regional prevalence and temporal trends [20, 28, 29, 31]. Contrary to the previous studies, which focused on hematologic malignancy or bloodstream infection [20, 28, 29, 31], our cohort includes all consecutive septic shock patients with FN, and aimed to select patients with ESBL-PE infection upon initial assessment in the ED. The consecutive inclusion of patients better reflects the real-world situation, and is more applicable in clinical practice.

Our study has several limitations. Although this study includes a unique cohort using a prospective septic shock registry, its retrospective design imposes intrinsic limitations of data gathering, analysis, and interpretation. Second, this study was conducted at a single tertiary center in South Korea and the epidemiology of ESBL-PE differs in Asia compared to that in other parts of the world [20].

Conclusions

ESBL-PE is not a common causative pathogen in patients with chemotherapy-induced FN in septic shock. Profound neutropenia at ED admission is an independent risk factor for ESBL-PE infections in our cohort. Considering the spread of carbapenem resistance and the importance of

appropriate antibiotic use in the treatment of septic shock patients [4, 5], further prospective studies are required to identify the predictors for ESBL-PE infection in patients with septic shock during FN. Profound neutropenia, an independent risk factor identified in our study, and the presence of some specific solid tumor might become adjunctive criteria that help physicians to identify patients who are most likely to benefit from early empirical carbapenem therapy.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose or any funding.

Statement of human and animal rights The institutional review board of Asan medical center approved the registry (study no.: 2015-1253). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained before data collection.

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