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Associated factors and clinical outcomes of bloodstream infection due to extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* during febrile neutropenia

Eli Ben-Chetrit[a], Mustafa Abed Eldaim[b], Maskit Bar-Meir[a], Mutaz Dodin[c], David E. Katz[b,*]

[a] Department of Infectious Diseases, Shaare Zedek Medical Center, affiliated with Hebrew University, Jerusalem, Israel
[b] Division of Internal Medicine D, Shaare Zedek Medical Center, affiliated with Hebrew University, Jerusalem, Israel
[c] Department of Hematology-Oncology, Shaare-Zedek Medical Center, affiliated with Hebrew University, Jerusalem, Israel

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ABSTRACT

Patients with neutropenia are vulnerable to serious infections. During the last decade, increased prevalence of extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae has affected immunocompromised patients. We conducted a single-center case–control study to evaluate factors associated with ESBL-positive bacteremia among neutropenic patients, and its clinical impact. The study included adult patients with hematologic or oncologic diseases diagnosed with ESBL-positive and ESBL-negative *Escherichia coli* or *Klebsiella pneumoniae* bacteremia during febrile neutropenia between January 2010 and October 2017 at the Shaare Zedek Medical Center, Jerusalem, Israel. Analyses included risk factors for ESBL-positive bacteremia, appropriateness of empiric antibiotics, mortality, length of stay, and intensive care unit (ICU) admission. Univariate and multivariate models were constructed. The cohort (80 patients), consisted of 54 ESBL-negative and 26 ESBL-positive Gram-negative bacteremia. Multivariate analysis suggested ESBL-positive bacteremia to be associated with long-term central venous catheter (CVC) (odds ratio (OR), 8.7; 95% confidence interval (CI), 1.6–48.1; P=0.01], index culture obtained 48 h post-admission (OR, 3.6; 95% CI, 1–12.3; P=0.04), and exposure to previous antimicrobial therapy (OR, 12.6; 95% CI, 2.1–74; P<0.01). There were no significant differences between groups with regard to length of stay, ICU admission, or mortality rates. Mortality was associated with high Pitt bacteremia score but not inappropriate empirical therapy. Previous antimicrobial therapy, long-term CVC, and hospital-acquired bacteremia were associated with ESBL bacteremia. Neutropenic patients with ESBL bacteremia have increased morality due to other factors than ESBL status. These findings should be validated in other centers and with larger populations.

1. Introduction

Patients with neutropenia are most vulnerable to serious infections. Previous reports suggest a prevalence of bacteremia among neutropenic patients (mostly secondary to hematologic malignancies) that ranges from 10% to 40%, and a crude mortality rate that may reach up to 40% [1–4]. Sepsis in neutropenic patients is largely attributed to translocation of Enterobacteriaceae from the damaged gastrointestinal tract to the bloodstream. During the last decade, the global increase in the prevalence of extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae has also affected immunocompromised patients. Recent studies in patients with hematologic malignancies reported worse outcomes, higher numbers of intensive care unit (ICU) admissions, and higher overall mortality rates after bacteremia with ESBL-positive versus ESBL-negative pathogens [4–9]. Inappropriate empirical antibiotic treatment of ESBL-positive infection has been repeatedly shown to be a risk factor for increased mortality [4–8]. In contrast, in non-neutropenic patients, some reports suggest that other factors such as a high Pitt bacteremia score, non-urinary source of infection, mechanical ventilation, and multiple co-morbidities are major contributors to worse outcomes [10–15]. These findings stress the significance of appropriate empiric antimicrobial agents in patients who virtually have no immune response.

The current Infectious Diseases Society of America (IDSA) guidelines recommend empiric therapy during febrile neutropenia, including antibiotic regimens that cover ESBL-positive pathogens. Most concerning are the high-risk patients, defined as those with

* Corresponding author. Division of Internal Medicine, Shaare Zedek Medical Center, 12 Shmuel Bait Street, PO Box 3235, Jerusalem 9103102, Israel.
E-mail address: dekatz1@gmail.com (D.E. Katz).

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'anticipated prolonged and profound neutropenia, hypotension, pneumonia, abdominal pain, or neurologic changes' [16]. We conducted a single-center study to evaluate factors associated with ESBL-positive bacteremia among neutropenic patients, as well as its impact on clinical outcome.

2. Methods

This study included all patients with hematologic or oncologic (solid tumors) diseases who were diagnosed with ESBL-positive and ESBL-negative *Escherichia coli* or *Klebsiella pneumoniae* bacteremia during febrile neutropenia between January 2010 and October 2017 at the Shaare Zedek Medical Center (SZMC), Jerusalem, Israel. Patients eligible for inclusion in the study were 18 years of age or older. Retrieval of demographic, clinical, and microbiologic data was performed retrospectively, utilizing the electronic medical record. Variables extracted included: age, sex, residence, underlying disease (hematologic or oncologic malignancy), chemotherapy treatment, previous hospitalization within 90 days, and exposure to antibiotics within the preceding 4 weeks. The impact of comorbidities was determined by the Charlson Comorbidity Index (CCI) [17].

Nosocomial bacteremia was defined as bacteremia occurring >48 h after admission to the hospital (index culture sampled 48 h after admission). Types of infection (i.e. pneumonia, intra-abdominal infection, urinary tract infection, soft-tissue infection, catheter-related bloodstream infection (CRBSI), and primary bacteremia) were determined based on clinical and microbiological findings. Presence of intravenous catheters during bacteremia was recorded. The Pitt bacteremia score was used to assess severity of illness, and was calculated at the onset of bacteremia (within 24 h before index culture date), using the following criteria: (1) oral temperature: 2 points for a temperature of ≤35°C or ≥40°C, 1 point for a temperature of 35.1–36.0°C or 39.0–39.9°C, and 0 points for a temperature of 36.1–38.9°C; (2) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mmHg, respectively; use of intravenous vasopressor agents, or systolic blood pressure <90 mmHg; (3) receipt of mechanical ventilation: 2 points; (4) cardiac arrest: 4 points; and (5) mental status: alert, 0 points; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points.

2.1. Definitions

An oral temperature above 38.0°C was considered as fever. Neutropenia was defined as an absolute neutrophil count (ANC) of <500 cells/mm^3 or a count of <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3 within the following 2 days. Neutropenia was considered severe if the ANC was <100 cells/mm^3.

2.2. Microbiology

The first positive blood culture for *E. coli* or *K. pneumonia* isolated from a patient with febrile neutropenia was termed as the index culture. Susceptibility testing and ESBL confirmation using the antimicrobial agent ceftazidime with and without clavulanic acid was performed according to the Clinical and Laboratory Standards Institute (CLSI) [18]. Strains showing 'intermediate' antimicrobial susceptibility profiles were considered as resistant isolates. Co-infections and polymicrobial bacteremia were considered in case of isolation of other pathogens from the index blood cultures. Patients with blood cultures that yielded one or more types of Gram-negative bacteria, at least one strain of which was an ESBL-producer, were included in the ESBL group. Contaminants were defined as coagulase-negative *Staphylococcus* species, *Propionibacterium* acnes, *Micrococcus* species, '*viridans*'-group streptococci, *Corynebacterium* species, or *Bacillus* species, not fulfilling CRBSI definition [19]. Fungal or viral co-infections were recorded as well if detected within 30 days of bacteremia.

2.3. Ethics

This study was approved by the local ethics committee (local reference number 249/16).

2.4. Outcome measures

Predisposing conditions associated with ESBL-positive bacteremia were sought. Appropriateness of empirical antibiotic treatment as defined by the organisms' antimicrobial susceptibilities (in vitro cultures), was evaluated. Cephalosporins aside from cefepime, were considered inappropriate in case of ESBL-positive bacteremia. Treatment response was defined as resolution of fever within 7 days of treatment. Two-week (attributable mortality) and 30-day mortality, length of stay (LOS), and ICU admission, were assessed.

2.5. Statistical analysis

Quantitative variables were compared using the two-sided *t*-test for two independent groups, and the Mann–Whitney test when the distribution of the tested variable was abnormal. Odds ratios (ORs) were calculated, and 95% confidence intervals (CIs) and *P*-values are presented. For qualitative variables, a χ^2-test or Fisher's Exact Test was used. Variables found statistically significant ($P<0.05$) in a univariate model were further examined using a multivariate logistic regression model (Enter selection method). The time to death was analysed with the use of Kaplan–Meier methods, and a two-sided log-rank test was used to compare the groups. All statistical analyses were carried out using SPSS software (version 21).

3. Results

Eighty-eight patients were identified during the study period. Eight patients (excluded from the final analysis) had no underlying hematologic or oncologic disease, and neutropenia was attributed to overwhelming Gram-negative sepsis. Within the included cohort (80 patients), 54 had ESBL-negative Gram-negative bacteremia and 26 had ESBL-positive Gram-negative bacteremia. Most patients in the study cohort (62/80), had an underlying hematologic disorder. There were no significant differences between the two groups with regard to mean age, sex, residence, underlying disease, timing of chemotherapy, CCI, severity of neutropenia, and Pitt bacteremia score (Table 1). *E. coli* and *K. pneumonia* bacteremia were detected in 48 and 32 patients, respectively. Twelve (25%) of the *E. coli* isolates and 14 (43.8%) of the *K. pneumoniae* isolates were ESBL-producing strains. *K. pneumoniae* was more common among ESBL-producing strains than *E. coli* ($P=0.09$). In both groups, the source of bacteremia was undetermined in most patients (79%).

The presence of central venous catheter (CVC) during bacteremia was significantly more prevalent within the ESBL-positive bacteremia group ($P<0.001$). Index culture obtained more than 48 h post-admission, as well as exposure to antimicrobial therapy up to 6 months prior to admission, were both significantly more common within the study group ($P<0.01$) (Table 1). Four patients who were previously colonized/infected with ESBL-pathogens had ESBL-positive bacteremia. There were only five cases of fungal infection within 30 days of bacteremia; four of them in the ESBL group ($P=0.04$).

Appropriate empirical antimicrobial therapy as determined by *in vitro* cultures, was administered in 13/22 (59.1%) neutropenic

Table 1
Demographic and clinical characteristics of patients with febrile neutropenia and extended-spectrum β-lactamase (ESBL)-negative and ESBL-positive *Escherichia coli* or *Klebsiella pneumoniae* bacteremia.

n (%)	ESBL-negative (*n*=54)	ESBL-positive (*n*=26)	*P*
Age (mean, SD)	65.9 ±15.3	63.8 ±13.7	0.6
Male	27 (50)	16 (61.5)	0.4
Residence			0.6
Home	53 (98.1)	25 (96.2)	
Nursing home	1 (1.9)	1 (3.8)	
Charlson Comorbidity Index (CCI)	5.2 ±2.9	4.9 ±2.5	0.6
CCI > 4	38 (70.4)	17 (65.4)	0.8
Pitt bacteremia score (mean ± SD)	2.3 ±2.5	2.5 ±2.2	0.8
Pitt bacteremia score ≥4	7 (13)	5 (19.2)	0.5
Likely source of infection			
CRBSI	1 (1.9)	1 (3.9)	
Urinary tract	4 (7.4)	1 (3.9)	
Intra-abdominal	0 (0)	3 (11.5)	
Pneumonia	4 (7.4)	1 (3.9)	
Soft tissue	2 (3.7)	0 (0)	
Primary/unknown	43 (79.6)	20 (76.9)	
Underlying disease			0.6
Hematologic	43 (79.6)	19 (73.1)	
Oncologic	11 (20.4)	7 (26.9)	
Status of underlying disease[a]			0.3
Advanced disease (metastatic or relapse)	31 (75.6)	20 (87)	
New diagnosis	10 (24.4)	3 (13)	
Bone marrow transplantation (autologous)	3 (5.6)	5 (19.2)	0.1
Pathogen			0.09
Escherichia coli	36 (66.7)	12 (46.1)	
Klebsiella pneumoniae	18 (33.3)	14 (53.9)	
Polymicrobial bacteremia[b]	16 (29.6)	6 (23)	0.3
Fungal infection within 30 days	1 (1.9)	4 (15.4)	0.04
Viral co-infection	6 (11.5)	3 (11.1)	1
Initial ANC during bacteremia, cells/mm^3 (mean, SD)	371 ±311	463 ±373	0.3
Deep neutropenia (<100 cells/mm^3) during bacteremia	19 (35.2)	9 (34.6)	1
Chemotherapy within 1 month	45 (83.3)	24 (92.3)	0.5
Chemotherapy within 6 months	32 (59.3)	16 (61.5)	1
Presence of long-term CVC during index culture	28 (53.9)	24 (92.3)	<0.001
CVC days before index culture[c] (mean, SD)	33.1 (29)	22.9 (26.4)	0.3
Admission days prior index culture (mean, SD)	6.4 ±10	11.5 ±10	0.03
Index culture >48 h	21 (38.9)	19 (73.1)	0.004
Previous admission (90 days)	36 (66.7)	20 (76.9)	0.4
Previous antimicrobial therapy (6 months)	30 (55.6)	24 (92.3)	<0.001
Previous (90 days) colonization/infection with an ESBL pathogen	0 (0)	4 (15.4)	NA

Data was available for 20/28 and 14/24 patients in the ESBL-negative and ESBL-positive groups, respectively. ANC, absolute neutrophil count; CCI, Charlson Comorbidity Index; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; SD, standard deviation.

[a] *n*=64 (remission 5; unavailable data 11).

[b] *Viridans streptococci, E. coli, K. pneumonia, Enterobacter sp., Bacteroides sp. Acinetobacter sp.*

patients with ESBL-positive bacteremia. Within the ESBL-negative bacteremia group, appropriate empirical therapy was administered in 51/52 (98.1%) of the patients (*P*<0.001) (Table 2). Figure 1 demonstrates the antimicrobial regimens that were administered empirically. Two patients (9.1%) with ESBL-positive bacteremia and seven patients (13.7%) in the control group were treated empirically with a carbapenem (*P*=0.7).

There were no significant differences between both groups with regard to additional outcomes such as length of stay, ICU admission, 2-week or 30-day mortality rates (Table 2).

Multivariate analysis suggested ESBL-positive bacteremia to be associated with the following factors: presence of long-term CVC (OR, 8.7; 95% CI, 1.6–48.1; *P*=0.01), index culture obtained 48 h post-admission (OR, 3.6; 95% CI, 1–12.3, *P*=0.04), and exposure to previous antimicrobial therapy within 6 months prior to admission (OR 12.6; 95% CI, 2.1–74, *P*<0.01) (Table 3). The analysis was adjusted for underlying disease, as the degree and duration of immunosuppression in hematologic patients is higher than in oncologic patients. Pathogen type was added to the analysis since the rate of *K. pneumoniae* was higher within the ESBL-positive group (Table 1). Interaction analyses between the terms did not affect the regression model. After adjusting for other risk factors

Table 2
Outcome measures of neutropenic patients with extended-spectrum β-lactamase (ESBL)-positive and ESBL-negative bacteremia.

n (%)	ESBL-negative (*n*=54)	ESBL-positive (*n*=26)	*P*
ICU admission	2 (3.7)	4 (15.4)	0.08
Length of stay (mean, SD)	20.8 ±23	26.1 ±21	0.3
Appropriate empirical antimicrobial therapy according to *in vitro* susceptibility testing[a]	51 (98.1)	13 (59.1)[b]	<0.001
Treatment response[c]	36 (69.2)	12 (54.6)	0.3
Two-week mortality[d]	8 (15.7)	5 (23.8)	0.6
30-day mortality[d]	11 (21.6)	6 (28.6)	0.7

ICU, intensive care unit; SD, standard deviation.

[a] Empirical antimicrobial therapy was not administered in three patients with ESBL-positive Gram-negative bacteremia. Two patients with ESBL-negative and one with ESBL-positive Gram-negative bacteremia were excluded due to polymicrobial bacteremia with pathogens resistant to empirical therapy (*Enterobacter cloacae, Acinetobacter baumanii,* and *Enterococcus faecalis*).

[b] Empirical treatment with a carbapenem was administered in only two patients.

[c] Resolution of fever within 7 days.

[d] Three patients with ESBL-negative Gram-negative bacteremia and five patients with ESBL-positive Gram-negative bacteremia died within 48 h of admission and were excluded from analysis.

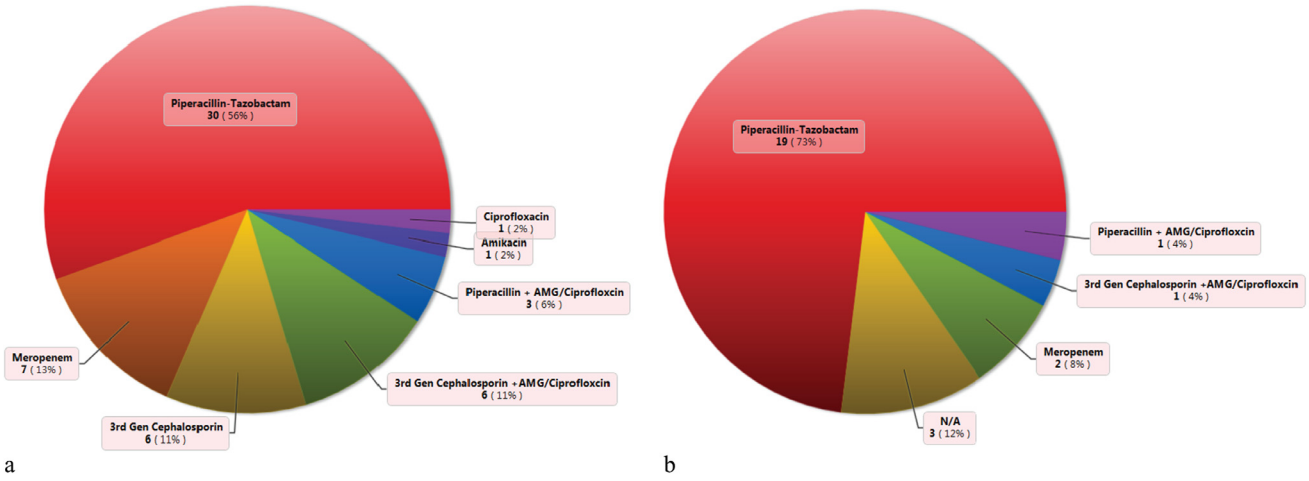

Figure 1. Empirical therapy administered to patients with ESBL-negative (panel a) and ESBL-positive (panel b) Gram-negative bacteremia (Gram-negative coverage only). Aminoglycoside; AMG.

Table 3
Factors associated with extended-spectrum β-lactamase (ESBL)-positive Gram-negative bacteremia.

Variable	Unadjusted analysis		Adjusted analysis	
	OR (CI)	*P*	OR (CI)	*P*
Underlying disease*	1.4 (0.5–4.3)	0.7	2.9 (0.7–12.9)	0.15
Klebsiella pneumoniae versus *Escherichia coli*	2.3 (0.9–6)	0.08	1.3 (0.4–4.3)	0.7
Index culture >48 h	4.3 (1.5–11.9)	0.008	3.6 (1.03–12.3)	0.04
Previous antimicrobial therapy (6 months)	9.6 (2–44.7)	0.002	12.6 (2.1–74)	0.005
Presence of CVC during index culture	11.1 (2.4–51.9)	0.003	8.7 (1.6–48.1)	0.01

CI, confidence interval; CVC, central venous catheter; OR, odds ratio.
* Hematologic versus oncologic.

Table 4
Risk factors associated with 2-week mortality in patients with febrile neutropenia and Gram-negative bacteremia.

Variable	Univariate analysis		Multivariate analysis	
	OR (CI)	*P*	OR (CI)	*P*
ESBL-positive bacteremia	1.7 (0.5–5.9)	0.5	2.9 (0.6–14.8)	0.2
Appropriate empirical antimicrobial therapy[a]	2.3 (0.3–19.5)	0.7	2.5 (0.2–32.5)	0.5
Charlson comorbidity index (CCI) >4	7.7 (0.9–63)	0.048	6.6 (0.7–60.7)	0.09[b]
Pitt bacteremia score ≥4	8.6 (1.3–57.8)	0.038	11 (1.3–98.9)	0.03[b]
Underlying disease	2.2 (0.6–8.5)	0.3	2.4 (0.5–11)	0.3

CI, confidence interval; ESBL, extended-spectrum β-lactamase; OR, odds ratio.
[a] Appropriate therapy based on in vitro susceptibility culture tests.
[b] Adjusted 30-day mortality risk factors included Charlson comorbidity index >4 and Pitt bacteremia score >4 (*P*=0.03 and *P*=0.024, respectively).

associated with 2-week and 30-day mortality, only high Pitt bacteremia score was significantly associated with 2-week mortality (Table 4). A Kaplan–Meier survival analysis is presented in Fig. 2. ESBL-positive versus ESBL-negative status did not impact mortality rate ($\chi^2 = 0.43$, P=0.5).

4. Discussion

The majority of reports that have examined outcomes of ESBL-positive Gram-negative bacteremia, included mostly immunocompetent patients [20–22]. In this study, we described a cohort of 80 immunocompromised adult patients (the majority due to hematologic malignancy) with febrile neutropenia and *E. coli* or *K. pneumoniae* bacteremia. Of them, 26 (32.5%) had ESBL-positive Gram-negative bacteremia.

Several factors associated with ESBL-positive Gram-negative bacteremia were observed, including index culture obtained 48 h post-admission, previous antimicrobial therapy and the presence of CVC (Table 3). The first two findings are well established in both immunocompetent and immunocompromised or neutropenic patients [5–8,23]. In contrast to other studies [24,25], previous admission, by itself, was not associated with ESBL-positive bacteremia in our cohort. Interestingly, only a few studies suggested the use of CVC during bacteremia to be associated with ESBL infection [26,27]. In our cohort, CVC was an independent risk factor for ESBL-positive bacteremia, although CRBSI was diagnosed in only one patient. Importantly, missed diagnoses of CRBSI events may have occurred, as long-term CVCs in neutropenic patients are not immediately extracted in cases of *E. coli* or *K. pneumoniae* bacteremia (in contrast to *Staphylococcus aureus*). Because the likely mechanism of Gram-negative bacteremia during febrile neutropenia is bacterial translocation from damaged mucosal surfaces of the skin or gut (after treatment with cytotoxic regimens), extraction of CVC was performed in many patients only several days after antimicrobial therapy was initiated, which could have negatively affected the yield of catheter-tip cultures.

All four patients in our cohort that were known to be either colonized or infected with an ESBL-positive pathogen within 90 days prior to admission, had ESBL-positive Gram-negative bacteremia. Previous colonization/infection with ESBL pathogens is a known risk factor for ESBL-positive Gram-negative bacteremia [25,28]. However, we did not include this risk factor in the analysis due to the small number of patients.

ESBL production was not associated with increased 2-week or 30-day mortality rate (Table 4, Fig. 2). This finding was surprising given the fact that almost 60% of the patients with ESBL-positive Gram-negative bacteremia were treated inadequately based on in vitro susceptibility testing (Table 2). Empirical antimicrobial therapy included piperacillin-tazobactam in 53% and 73% of the patients with ESBL-negative and ESBL-positive bacteremia, respectively (Fig. 1). This regimen is consistent with the Infectious Diseases Society of America Guidelines for the use of antimicrobial agents in neutropenic patients with cancer [16]. Other regimens included meropenem or third-generation cephalosporins (primarily ceftazidime). Yet, the rather low rate of adequate empirical therapy (per in vitro culture) in the ESBL-positive group (59%) was unexpected. Sixteen (61%) isolates were resistant to

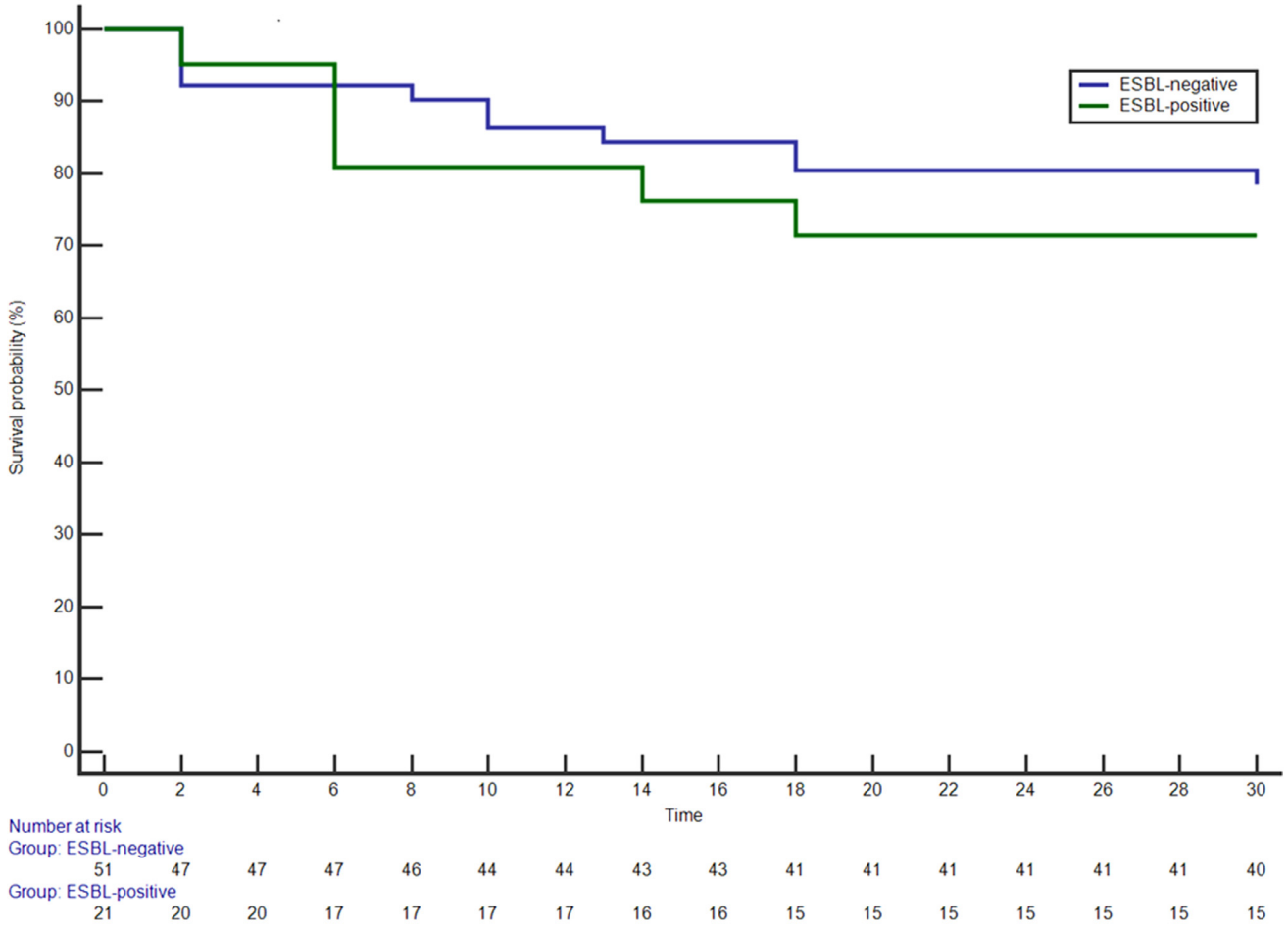

Figure 2. Kaplan-Meir estimates of overall survival in patients with ESBL-negative and ESBL-positive Gram-negative bacteremia (χ^2=0.43, P=0.5).

piperacillin-tazobactam (data not shown). This may imply previous exposure to antibiotics and resistance selection (as demonstrated in this study group), and suggests that carbapenems should have been administered empirically to these patients.

In the recent prospective Merino trial, definitive treatment with a carbapenem (vs. piperacillin-tazobactam) was shown to improve 30-day survival, even when piperacillin-tazobactam susceptibility was demonstrated in ceftriaxone-resistant *E coli* or *K. pneumoniae* bacteremia [29]. This outcome may be more pronounced in immunocompromised patients with febrile neutropenia, or those with higher severity of illness. Most isolates in the ESBL-positive group in our study were resistant to piperacillin-tazobactam; therefore, we could not address the issue of preferred definitive therapy (i.e. piperacillin-tazobactam vs. meropenem) as further subgroup analyses were limited by the small sample size. However, appropriateness of empirical therapy was not associated with increased mortality in our study. Although ESBL production was previously reported to be associated with a delay in effective therapy and increased mortality [6,30], other reports did not demonstrate this [5,8]. Specifically, in a study of ESBL-bacteremia in neutropenic patients, 30-day mortality rates for ESBL-positive and ESBL-negative bacteremia were not significantly different, and inadequate empirical therapy had no effect on mortality [8]. Similarly, in our study, the most significant factor associated with 2-week or 30-day mortality was Pitt bacteremia score ≥4 at infection onset (Table 4, Fig. 2). This significant association was also demonstrated after excluding patients who died within 48 h of admission. The severity of illness at onset of infection (as reflected by the high Pitt bacteremia score or septic shock during bacteremia) is an independent risk factor for death in bacteremic patients including those with ESBL-producing pathogens [5,31,32]. The contribution of ESBL production to mortality risk, even with neutropenic patients, may be less pronounced than previously thought. Administration of appropriate empirical antimicrobial therapy is clearly important, but adequate and timely resuscitation, as well as source control, is crucial [33].

Our study has several limitations. First, sample size was relatively small and therefore analysis was subject to confounding. However, our two groups were balanced with regard to age, CCS, and Pitt bacteremia score (Table 1), and we applied statistical modeling to help control for confounding. Second, as this was a retrospective study, some data was lacking; e.g., the exact hour of antibiotic administration. However, administration of antimicrobial therapy for in-patients with febrile neutropenia is rarely delayed, and we believe that any difference in time to empirical antibiotic administration would not be significant between the groups. In addition, the impact of delay in administration of appropriate antibiotic should be reflected, at least partially, in our analysis of appropriateness of empirical antibiotics (Table 2). Third, data related to the likely source of bacteremia was missing. However, primary bacteremia (in particular, Gram-negative bacteremia) in neutropenic patients is often encountered. Fourth, our data is based on the local epidemiology of a single center and cannot be generalized. Nevertheless, similar risk factors and outcomes were demonstrated elsewhere. Finally, we did not address the impact of definitive therapy. We aimed to assess the significance of appropriate empirical therapy. Once antibiotic susceptibility results were available, usually within 48 h of the index culture, patients were

treated adequately. Most patients with ESBL-positive bacteremia were switched to a carbapenem (data not shown).

This study presents factors associated with ESBL-positive Gram-negative bacteremia and patient outcomes during febrile neutropenia, in a unique, immunocompromised patient population. The most important variables found to be associated with ESBL-bacteremia were previous antimicrobial therapy, presence of CVC during bacteremia, and index culture drawn more than 48 h post-admission. Mortality was associated with a high Pitt bacteremia score but not inappropriate empirical therapy. These results should be validated in other centers and with larger populations.

Declarations

Funding

None

Competing Interests

None

Ethical Approval

Ethical approval was provided by the local Helsinki ethics committee.

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