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Bloodstream Infections by Extended-spectrum β-lactamase-producing *Klebsiella* Species in Children

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Abstract

Infections caused by resistant Gram-negative bacteria are a serious public health problem, with *Klebsiella* spp. being the most common cause and increasing over the years. There is a striking increase in antibiotic resistance worldwide. The aim of this study was to retrospectively evaluate the characteristics and treatment of bloodstream infections (BSIs) caused by *Klebsiella* spp. and to identify possible risk factors for extended-spectrum β-lactamase (ESBL) resistance in our hospital between August 2019 and March 2023. Of 250 *Klebsiella* isolates, 112 (44.8%) were ESBL producers and 138 (55.2%) were ESBL nonproducers. Catheter-related BSIs (CRBSIs) accounted for 49.6% of infections and were more common in the ESBL nonproducer group. Most of the *Klebsiella* spp. were K. pneumoniae (233/250). Most of the infections were healthcare-associated infections (85.6%). Most patients had an underlying disease, the most common underlying disease in the ESBL-producing group was neurometabolic disease (26.8%), whereas in the ESBL-non-producing group it was malignancy (35.5%). The median age of the ESBL-producing group was 14 months and was younger (p=0.01). Previous antibiotic use in the last 30 days, especially aminoglycosides (p<0.006), β-lactam-β-lactamase inhibitor combinations (p<0.001) and cephalosporins (p<0.001), increased ESBL-resistant infection. Use of β-lactam-β-lactamase inhibitor combinations in the last 30 days increased the risk of ESBL resistance by approximately 7.4 times, and cephalosporins increased the risk by 5 times. In the ESBL-producing group, the median duration of treatment was longer at 14 days (p=0.01), and carbapenems were most commonly used (p<0.001). Thrombocytopenia (p=0.003), elevated C-reactive protein (p<0.001), CRBSI (p=0.009), presence of central venous catheter (p=0.03), urinary catheter (p<0.001), mechanical ventilation (p<0.001), intensive care admission (p=0.005), previous use of carbapenems, aminoglycosides, fluoroquinolones in the last 30 days (p=0.003, p=0.001, p=0.006, respectively) and colistin treatment (p<0.001) increased the risk of mortality. The 28-day mortality rate was 11.6%. Appropriate use of narrow-spectrum antibiotics and reduction of invasive procedures is important in reducing ESBL resistance and BSI-related mortality.

Keywords: Extended spectrum β-lactamase, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, children

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Introduction

Infections caused by resistant Gram-negative microorganisms are a serious public health problem due to the lack of treatment options, insufficient clinical data and high mortality, especially in children.[1] There is a striking increase in antibiotic resistance worldwide. Bacterial resistance patterns change over time and across geographic regions. Extended-spectrum β-lactamase (ESBL) is class A β-lactamases, a rapidly evolving group of β-lactamases with ability to hydrolyze and cause resistance to the oxy-imino cephalosporins (cefotaxime, ceftazidim, ceftriaxone, cefuroxime, and cefepime) and monobactams (aztreonam).[2] The emergence of ESBL-producing bacteria occurred in the 1980s; nosocomial infections due to ESBL-producing *K. pneumoniae* strains have increased since the 1990s, while community-acquired infections caused by ESBL-producing bacteria have increased since 2000.[3] ESBL-producing *Klebsiella spp.* are the predominant cause of childhood infections and pose significant challenges such as development of adverse outcomes, treatment failure due to multidrug resistance, high morbidity and mortality.[2,4]

Klebsiella spp. is a common and severe pathogen of bloodstream infections (BSIs) due to Gram-negative bacilli.[5-10] *K. pneumoniae* is an important cause of human infections among all *Klebsiella* species, followed by *K. oxytoca, K. ozaenae,* and *K. rhinoscleromatis*.[2] Infections due to ESBL-producing *Klebsiella* tend to have higher mortality rates and longer hospital stays after infection compared to children with BSI due to non-ESBL-producing isolates.[6,11] Although it has been studied in many studies for adults, it is still a serious concern for children on few pediatric studies.

The aim of this study was to determine the characteristics, risk factors, and outcomes of BSIs caused by *Klebsiella spp.* in a tertiary care pediatric hospital, to assess risk factors for BSI caused by ESBL-producing *Klebsiella* in children, and to compare them with ESBL-non-producing *Klebsiella*.

Material and Method

In our study, blood cultures sent between August 2019 and March 2023 in Ankara City Hospital with a capacity of 610 beds were retrospectively analyzed. The results of blood cultures and catheter cultures collected from children aged 1 month to 18 years in the pediatric intensive care unit (PICU), pediatric surgical service and intensive care unit, pediatric burn unit, bone marrow transplant unit, palliative intensive care unit and pediatric services of our hospital were scanned from the registry systems.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Ankara City Hospital Ethic Commitee (decision no: E2-23-4168, date: 26.05.2023).

The Study Group

In blood cultures and catheter cultures, *Klebsiella spp.* (*K. pneumoniae, K. oxytoca*) culture results, culture antibiograms, and patient files were analyzed using computer recording systems. Demographic characteristics (age, gender), hospital inpatient service, underlying disease, mechanical ventilation, presence of central venous catheter, presence of urinary catheter, feeding with percutaneous endoscopic gastrostomy, treatment received, presence of neutropenic fever, and antimicrobial exposure (during the previous 30 days were: carbapenems, fluoroquinolones, glycopeptides, cephalosporins, aminoglycosides, colistin, β-lactam-β-lactamase inhibitor combinations and exposure to combined antimicrobials) were assessed. Duration of treatment, time to culture negativity, type of infection [BSI, catheter-related BSI (CRBSI)], mortality in the last 28 days, leukocyte count, neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP) level, and culture antibiogram results were recorded. If a patient had more than one episode of *Klebsiella* infection, only the first episode was included to avoid misinterpretation in the risk factor analysis. Results of polymicrobial cultures were not included. Because some patients died before culture negativity was confirmed and the treatment period was completed, treatment periods and time to first culture negativity were not included in the evaluation of these patients.

Culture antibiograms of patients with *Klebsiella spp*. in blood and catheter cultures were examined. Carbapenem-resistant, both carbapenem-resistant and ESBL-resistant *Klebsiella* species were excluded from the study to avoid confounding risk factors and mortality outcomes. ESBL-producing *Klebsiella* and ESBL-non-producing culture results were included in the study.

Definitions

The definition of nosocomial infections was made according to the surveillance diagnostic criteria determined by the Centers for Disease Control and Prevention (CDC) in the United States.[12]

A laboratory-confirmed BSI was defined according to the followings: a) the patient has a recognized pathogen identified from one or more blood specimens by a culture or non-culture based microbiological testing method which is performed for purposes of clinical diagnosis or treatment, and b) organism (s) identified in blood which is not related to an infection at another site.[13]

A definitive diagnosis of CRBSI requires that the same organism is isolated from at least 1 peripheral blood culture and from a culture of the catheter tip, or that two concurrent positive blood cultures obtained from the catheter hub and peripheral vein meet the CRBSI criteria.[13]

Microbiological Methods

Samples were inoculated on routine 5% sheep blood agar and MacConkey agar. After 16-24 hours of incubation at 37 °C, the growing isolates were identified with VITEK® MS (bioMérieux, France). Antimicrobial susceptibility profiles of the isolates of *Klebsiella spp* were determined by VITEK® 2 Compact (bioMérieux

Vitek, Hazelwood, MO, ABD) and interpreted based on the Clinical and Laboratory Standards Institute Criteria for other non-Enterobacteriaceae. Antibiotic susceptibility tests were performed in accordance with the European Committee on Antimicrobial Susceptibility Testing Enterobacterales guidelines.[14]

Statistical Analysis

All statistical analyzes were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc). The data of the patients were collected retrospectively from hospital records. The distribution of data was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as numbers and percentages. Continuous data are presented as medians. The medians of parameters were compared using the Mann-Whitney U test. Chi-square test was used in comparison of categorical variables between independent groups. Multivariate logistic regression analysis was used to determine the effect of risk factors on carbapenem resistance and mortality. The results of the regression analysis were given as odds ratio (OR) and 95% confidence interval (CI). P<0.05 was considered statistically significant.

Highlights

- *Klebsiella* is the most common Gram-negative pathogen causing healthcare-associated infections, and resistance rates are increasing every year.
- Neurometabolic diseases, previous use of aminoglycosides, β-lactam-β-lactamase inhibitor combinations and cephalosporins in last 30 days has been associated with bloodstream infection (BSI) by extended-spectrum β-lactamase-producing *Klebsiella* spp.
- Catheter-associated BSIs, indewelling devices, intensive care unit patients, history of carbapenem, aminoglycoside and fluoroquinolone use, treatment with colistin, thrombocytopenia and elevated C-reactive protein are associated with mortality in *Klebsiella* spp. BSIs.

Results

A total of 250 pediatric patients with *Klebsiella spp.* isolates in BSIs were included in the study (**Figure 1**). One hundred thirty-eight isolates (55.2%) were ESBL nonproducers and 112 (44.8%) were ESBL producers. CRBSIs were 49.6% of the whole infections. While CRBSI was more common in the ESBL-non-producing group (52.9%), BSI was more common in the ESBL-producing group (54.5%). Most of the *Klebsiella spp.* were *K. pneumoniae* (233/250), while most of the *K.oxytoca* were ESBL nonproducers (13/17). Eighty-five patients (34%) had febrile neutropenia, and the majority were in the ESBL-non-producing group (53/85) (**Table 1**). The infection was hospital-acquired or healthcare-associated in 214 (85.6%) children and community-associated in 36 (14.4%) children.

Underlying medical conditions/ diseases were not significantly different between two groups. ESBL-producing group displayed 26 (23.2%) malignancy, 30 (26.8%) neurometabolic diseases, 8 (7.1%) immunsupressed states, 14 (12.5%) cardiovascular diseases, 6 (5.4%) bronchopulmonary diseases, 13 (11.6%) surgical conditions and ten (9%) patients had not any underlying diseases. ESBL-non-producing group displayed 49 (35.5%) malignancy, 32 (23.2%) neurometabolic diseases, 11 (8%) immunsuppressed states, 12 (8.7%) cardiovascular diseases, 3 (2.2%) bronchopulmonary diseases, 16 (11.6%) surgical conditions and 2 (1.4%) patients had not any underlying diseases. There was no underlying disease in 9% of the ESBL-producing group, 1.4% in the ESBL-non-producing group. Approximately one-third (35.7%) of the ESBL-producing group were hospitalized in the intensive care unit (**Table 1**).

Median age of patients was 14 months in the ESBL-producing group, and patients with ESBL-producing isolates were younger than ESBL-non-producers

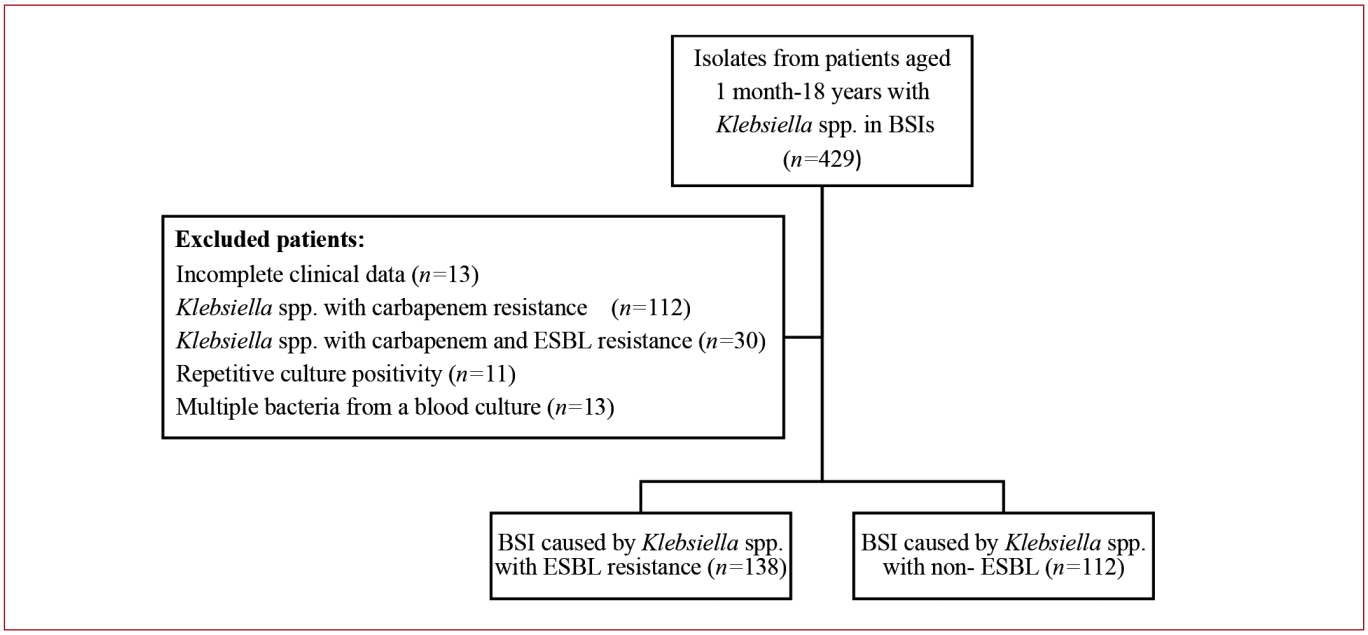

Figure 1. Flowchart of the selection process

ESBL; Extended spectrum beta-lactamase, BSI; Bloodstream infection

Table 1.
Demographics and clinical characteristics, treatment, and outcome of patients

	ESBL (-) n=138	ESBL (+) n=112	p
Age (months), median (min-max)	24 (1-214)	14 (1-224)	**0.01**
Gender, female/male	52/86	57/55	**0.03**
Underlying disease, n (%)	-	-	0.37
Malignancy	49 (35.5)	26 (23.2)	-
Immunosuppressed situations	11 (8)	8 (7.1)	-
Neurologic/metabolic disorders	32 (23.2)	30 (26.8)	-
Cardiovascular diseases	12 (8.7)	14 (12.5)	-
Bronchopulmonary diseases	3 (2.2)	6 (5.4)	-
Surgical conditions (e.g. burn, abdominal surgery)	16 (11.6)	13 (11.6)	-
Other	13 (9.4)	5 (4.5)	-
None	2 (1.4)	10 (9)	-
The type of infection	-	-	0.24
Bloodstream infection	65 (47.1)	61 (54.5)	-
Catheter-related bloodstream infection	73 (52.9)	51 (45.5)	-
Wards, n (%) of patients	-	-	0.56
Pediatric intensive care unit	37 (26.8)	40 (35.7)	-
Hematology oncology department	38 (27.5)	28 (25)	-
Pediatric surgery unit	13 (9.4)	10 (8.9)	-
Paediatrics department	37 (26.8)	29 (25.9)	-
Pediatric burn unit	5 (3.6)	2 (1.8)	-
Pediatric bone marrow transplantation unit	8 (5.8)	3 (2.7)	-
Medical devices present at the onset of infection, n (%) of patients			
Central venous catheter	96 (50.5)	66 (51.1)	0.08
Mechanical ventilation	12 (6.12)	14 (10.8)	0.32
Percutaneous endoscopic gastrostomy	9 (4.59)	6 (4.6)	0.7
Urinary catheter	20 (10.2)	11 (8.5)	0.26
Neutropenic fever	53 (38.4)	32 (28.5)	0.1
The history of antibiotic use in the last 30 days, n (%)			
Yes	18 (13)	63 (56.2)	**<0.001**
Use of combined antibiotics	5 (3.6)	10 (8.9)	0.07
Carbapenems	7 (5)	12 (10.7)	0.09
Aminoglycosides	2 (1.45)	10 (8.9)	**0.006**
β-lactam- β-lactamase inhibitor combinations	5 (3.6)	21 (18.7)	**<0.001**
Cephalosporins	6 (4.34)	28 (25)	**<0.001**
Glycopeptides	4 (2.9)	3 (2.6)	0.91
Fluoroquinolones	0	1 (0.89)	0.26
Colistin	1 (0.7)	1 (0.89)	0.88
Initial culture negativity (day), median (min-max)	2 (1-7)	2 (1-10)	0.08
Microorganism	-	-	0.06
Klebsiella pneumoniae	125 (90.6)	108 (96.4)	-
Klebsiella oxytoca	13 (9.4)	4 (3.6)	-
Initial leukocyte counts (mm^3), median (min-max)	7840 (10-23400)	11820 (40-59090)	0.09
Initial neutrophil counts (mm^3), median (min-max)	5430 (0-40190)	6720 (10-50490)	0.39
Initial lymphocyte counts (mm^3), median (min-max)	1210 (0-8980)	2180 (40-10580)	**0.03**
Initial thrombocyte counts ($x10^9/L$), median (min-max)	210 (2-800)	222 (6-1006)	0.28
CRP levels (mg/L), median (min-max)	68 (0-460)	74 (0-424)	<0.95
The duration of treatment (day), median (min-max)	12 (3-26)	14 (3-32)	**0.01**
Antibiotics used in treatment			
Carbapenems	72 (52.1)	84 (75)	**<0.001**
Aminoglycosides	48 (34.8)	44 (39.2)	0.46
Cephalosporins	22 (15.9)	12 (10.7)	0.23
Fluoroquinolones	6 (4.3)	2 (1.7)	0.25
Colistin	10 (7.2)	11 (9.8)	0.46
β-lactam- β-lactamase inhibitor combinations	32 (23.1)	11 (9.8)	**0.005**

Min-max; Minimum-maximum, CRP; C-reactive protein, ESBL; Extended spectrum beta-lactamase

(p=0.01). Most patients in the ESBL-non-producing group were males (86/138), and there was a significant difference between the groups in terms of gender (p=0.03). We performed analysis on the relationship of previous antibiotic usage before the identification of BSI. Use of antimicrobial treatment during the last 30 days was significantly different between ESBL-producing and ESBL-non-producing groups, 63/112, and 18/138, respectively (p<0.001). In the ESBL-producing group, 49 patients had not received any antibiotic treatment in the last 30 days. When analysis of antibiotic regimens was considered, previous aminoglycoside, β-lactam-β-lactamase inhibitor combinations, and cephalosporin use were higher in patients with ESBL-producing isolates than in those with ESBL-non-producing isolates (p=0.006, p<0.001, p<0.001, respectively) (**Table 1**).

Logistic regression analysis showed a significant correlation between ESBL resistance and two variables: β-lactam- β-lactamase inhibitor combinations exposure during the last 30 days (OR 7.425; CI 1.229-44.849; p=0.02) and cephalosporin exposure during the last 30 days (OR 5.063; CI 1.062-24.136; p=0.04). According to this result, the use of β-lactam- β-lactamase inhibitor combinations in the last 30 days increased the risk approximately 7.4 times, and the use of cephalosporins increased the risk 5 times for ESBL resistance (**Table 2**).

Although the lymphocyte count was lower in the ESBL-non-producing group (p=0.03), there was no significant difference between the two groups in neutrophil, leukocyte, platelet counts and CRP levels.

The duration of treatment was statistically significantly higher in the ESBL-producing group (p=0.01). In the treatment, carbapenem (p<0.001) was used more frequently in the ESBL-producing group, while β-lactam-β-lactamase inhibitor combinations were used more frequently in the ESBL-non-producing group (p=0.005).

The 28-day mortality rate was 11.6%. While the mortality rate in the ESBL-producing group was 12.5% (14/112), it was 10.8% (15/138) in the ESBL-non-producing group, and there was no significant statistical difference. The comparison of demographic, clinical characteristics and laboratory findings of patients according to the mortality group (MG) in **Table 3**. The platelet counts were statistically significantly lower in the MG group (p=0.003) and the CRP value was found to be higher in MG (p<0.001). CRBSI had a higher mortality rate than BSI (72.4%) (p=0.009). A central venous catheter was in 64.8% of all patients, and mortality was higher in these patients (p=0.03). Also, mechanical ventilation and presence of a urinary catheter were statistically significantly higher in MG (p<0.001, p<0.001, respectively). Mortality was more common in patients in intensive care (p=0.005). While mortality rates were higher in patients with neurometabolic disease (27.6%) and cardiovascular disease (27.6%), the difference was not statistically significant (p=0.055). While underlying immunosuppressed conditions and malignancy did not increase mortality, the presence of neutropenic fever did not increase mortality either (p=0.19). Mortality was higher in those who used carbapenem (p=0.03), aminoglycoside (p=0.01) and fluoroquinolone (p=0.006) in the last 30 days. In terms of antibiotic used in treatment, a statistically significant lower usage of cephalosporin was observed in MG (p=0.02), while colistin was statistically higher in MG (p<0.001). In MG, ESBL resistance was observed in 14/29 patients (p=0.68). In the multivariate logistic regression analysis between clinical variables and mortality, thrombocyte count (OR, 0.984: 95% CI, 0.973-0.995; p=0.005) was found to be an independent predictor of mortality (**Table 4**).

Table 2.
Multivariate analysis for ESBL resistance

	OR	95% CI	p
Initial lymphocyte counts	1	1-1	0.76
Antibiotic exposure during the last 30 days			
Yes	1.748	0.432-7.069	0.43
β-lactam- β-lactamase inhibitor combinations	7.425	1.229-44.849	**0.02**
Aminoglycosides	2.832	0.379-21.187	0.31
Cephalosporins	5.063	1.062-24.136	**0.04**

OR; Odds ratio, CI; Confidence interval, ESBL; Extended spectrum beta-lactamase

Discussion

BSIs caused by ESBL-resistant *Klebsiella spp.* are a growing public health concern worldwide with significant morbidity and mortality in children.[15,16] It is important to know the etiologic and demographic characteristics, predisposing factors, and possible antibiotic susceptibility in children because of the high mortality rates, prolonged hospital stays, and limited treatment strategies. Statistics vary widely from continent to continent, from center to center, and over the years. According to the 2020 report of the Central Asian and European Surveillance of Antimicrobial Resistance study, which also includes our country, ESBL resistance in *K. pneumoniae* strains in our country, which was 59% in 2013, gradually increased until 2019 and became 73%.[8] This resistance rate was 89% in Russia in 2020.[17] In the present study, we observed 44.8% ESBL production in *Klebsiella spp.*, causing BSI. In the study by Park et al.[16], ESBL resistance in children with *K. pneumoniae* bacteremia was 35.7% (30/84). In a previous study conducted in our country, ESBL resistance in BSIs due to *K. pneumoniae* in children was 62%.[6] Unlike these studies, our study also included *K. pneumoniae* and *K. oxytoca*, and most of the *K. oxytoca* isolates did not produce ESBL. In addition, the lower ESBL resistance in *Klebsiella* species in our study may be related to the implementation of a strict antimicrobial stewardship program to reduce excessive antibiotic prescribing in hospitalized patients and the fact that only BSIs were evaluated in the study.

In some studies, almost all patients had underlying disease,[16,18,19] while in some studies, patients had underlying diseases, although at lower rates, more in ESBL-producing patients.[6,20] In our study, patients without underlying diseases were more common in the ESBL producing group. It should be considered that children without underlying disease may also have ESBL-resistant BSIs, and empirical treatment should be initiated accordingly, especially in severe patients.

Table 3.
Demographics, clinical characteristics and laboratory findings characteristics of patients according to mortality

	Survival (n=221)	Death (n=29)	p
Age (months) (median)	16 (1-224)	12 (2-212)	0.78
Gender, F/M	96/125	13/16	0.88
Leukocyte counts (mm^3) Median (min-max)	9334 (10-59090)	14530 (40-41480)	0.17
Neutrophil counts (mm^3), Median (min-max)	6280 (0-50490)	10970 (0-38600)	0.09
Lymphocyte counts (mm^3) Median (min-max)	2080 (0-10580)	1540 (0-9080)	0.18
Thrombocyte counts ($x10^9$/L), Median (min-max)	220 (6-1006)	105 (2-602)	**0.003**
CRP (mg/L), median (min-max)	71 (0-438)	131 (0-460)	**<0.001**
Underlying disease	-	-	0.055
Malignancy	68 (30.8)	7 (24.1)	-
Immunosuppressed situations	17 (7.7)	2 (6.9)	-
Neurologic/metabolic disorders	54 (24.4)	8 (27.6)	-
Cardiovascular diseases	18 (8.1)	8 (27.6)	-
Bronchopulmonary diseases	9 (4.1)	0	-
Surgical conditions (e.g. burn, abdominal surgery)	27 (12.2)	2 (6.9)	-
Other	28 (12.7)	2 (6.9)	-
The type of infection	-	-	**0.009**
Bloodstream infection	118 (53.4)	8 (27.6)	-
Catheter-related bloodstream infection	103 (46.6)	21 (72.4)	-
Wards, n (%) of patients	-	-	**0.005**
Pediatric intensive care unit	59 (26.7)	18 (62.1)	-
Hematology oncology department	62 (27.1)	4 (13.8)	-
Pediatric surgery unit	23 (10.4)	0	-
Paediatrics department	61 (27.6)	5 (17.2)	-
Pediatric burn unit	6 (2.7)	1 (3.4)	-
Pediatric bone marrow transplantation unit	10 (4.5)	1 (3.4)	-
Microorganism	-	-	0.12
Klebsiella pneumonia	204 (92.3)	29 (100)	-
Klebsiella oxytoca	17 (7.7)	0	-
Medical devices present at the onset of infection, n (%) of patients			
Central venous catheter	138 (62.4)	24 (82.7)	**0.03**
Mechanical ventilation	1 (0.4)	25 (86.2)	**<0.001**
Percutaneous endoscopic gastrostomy	14 (6.3)	1 (3.4)	0.53
Urinary catheter	21 (9.5)	10 (34.4)	**<0.001**
Neutropenic fever	72 (32.5)	13 (44.8)	0.19
The history of antibiotic use in the last 30 days, n (%)			
Yes	69 (31.2)	12 (41.3)	0.27
Use of combined antibiotics	11 (5)	4 (13.7)	0.06
Carbapenems	14 (6.3)	5 (17.2)	**0.03**
Aminoglycosides	8 (3.6)	4 (13.8)	**0.01**
β-lactam- β-lactamase inhibitor combinations	23 (10)	3 (10.3)	0.99
Cephalosporins	32 (14.4)	2 (6.9)	0.26
Glycopeptides	5 (2.2)	2 (6.9)	0.15
Fluoroquinolones	0	1 (3.4)	**0.006**
Colistin	1 (0.4)	1 (3.4)	0.08
Antibiotics used in treatment			
Carbapenems	138 (62.4)	18 (62)	0.96
Aminoglycosides	86 (38.9)	6 (20.6)	0.056
Cephalosporins	34 (15.3)	0	**0.02**
Fluoroquinolones	8 (3.6)	0	0.29
Colistin	13 (5.8)	8 (27.5)	**<0.001**
β-lactam- β-lactamase inhibitor combinations	40 (18)	3 (10.3)	0.29
ESBL resistance	98 (44.3)	14 (48.2)	0.68

CRP; C-reactive protein, ESBL; Extended spectrum beta-lactamase, Min-max; Minimum-maximum, F/M: Female/male

In studies, malignancy patients were more common in *Klebsiella* BSIs and especially in the ESBL-producing group.[16,20] In the present study, the most common underlying disease was malignancy in all patients and in the ESBL-non-producing group, while neurometabolic disease was more common in the ESBL-producing patient group, similar to a study conducted in our country.[6] In an adult study in which data from 33 hospitals from 12 countries were analyzed, ESBL-producer *K.pneumoniae* BSIs were mostly detected in patients with neurometabolic and cardiovascular diseases.[21] In our study, mortality was also higher in patients with neurometabolic and cardiovascular diseases. All these results show that apart from malignancy patients, patients with neurometabolic and cardiovascular diseases should be cautioned in terms of resistance and high probability of mortality.

In addition, febrile neutropenia was more common in the ESBL non-producing group in our study. It was thought that the reason for this was that most of the patients with malignancy were in the ESBL nonproducing group.

Similar to studies in our country and other countries, younger patients were at a significantly higher risk of BSI with ESBL-producing *Klebsiella spp.* The median age of the ESBL-producing group was 14 months.[6,22]

In our study, the overall mortality rate in BSIs due to *Klebsiella spp.* was 11.6%, and although analysis did not reveal statistical significance, 28 day mortality was relatively higher in patients with ESBL-producing isolates (12.5%). While mortality rates in most adult studies (23.9-47.9%) are higher than in studies including children (17-26.6%), these rates vary by years, countries, and centers.[6,16,18,21,23-27] This mortality was lower compared with other studies. Even though our hospital is a tertiary care hospital where serious patients are referred, it may be associated with low mortality, early initiation of effective treatment due to a good surveillance network, higher proportion of patients without underlying disease, fewer patients with malignancy, and febrile neutropenia than other studies. According to the results of the CDC National and State Healthcare-Associated Infections Progress Report, there was a 7% increase in central line-associated BSIs during the Coronavirus disease-2019 (COVID-19) pandemic.[28,29] In our study, which included the duration of the COVID-19 pandemic, about half of the patients had CRBSI. In this study, although ESBL resistance was lower in catheter-associated BSIs, the mortality rate was higher during the pandemic period. This finding may be related to the density of healthcare services and deficiencies in routine healthcare services such as catheter care. There is also a need to discontinue catheter use early in catheter infections, especially with resistant organisms, and to understand the importance of catheter care.

Table 4.
Multivariate analysis for mortality

	OR	95% CI	p
Thrombocyte counts	0.984	0.973-0.995	**0.005**
CRP	0.996	0.986-1.006	0.42
The type of infection	0.245	0.007-9.101	0.44
Clinic of pediatric surgery unit	0.384	0.038-3.926	0.42
The presence of central venous catheter	2.617	0.050-135.689	0.63
The presence of urinary catheter	2.081	0.207-20.885	0.53
Colistin used in treatment	9.334	0.173-504.986	0.27

OR; Odds ratio, CI; Confidence interval, CRP; C-reactive protein

We found a significant association between BSIs with ESBL-producing *Klebsiella spp.* and previous antibiotic use, especially aminoglycosides, β-lactam-β-lactamase inhibitor combinations, and cephalosporins. Among previously used antibiotics, cephalosporin and β-lactam-β-lactamase inhibitor combinations have been associated with a significantly increased risk of BSIs in ESBL-producing isolates. The association between previous antibiotic use and ESBL-producing *Klebsiella* infections in children is supported by some studies. The body of work supporting an association between previous antibiotic use and infection with ESBL-producing *Klebsiella spp.* in children is not as extensive as in adults, but it is growing and much of it focuses on urinary tract infections and prophylaxis.[6,20,30-34] Supporting the results of our study, previous studies have shown that prior use of cephalosporins and aminoglycosides is associated with ESBL-resistant infections in children with BSIs caused by *Klebsiella*.[6,20,26,27,34] This study also showed that use of β-lactam-β-lactamase inhibitor combinations in the previous 30 days is also a risk for ESBL-producing *Klebsiella* BSIs. Zerr et al.[34] showing that use of β-lactam-β-lactamase inhibitor combinations in the last 30 days increases ESBL resistance in *Klebsiella* infections is similar to our data. Our study differs in that the number of patients was higher and only BSIs were included. In addition, aminoglycoside use was higher in the MG in our study, as were carbapenems and fluoroquinolones.

While there are studies showing that the presence of urinary and central venous catheters, mechanical ventilation, and PICU hospitalization are more common in ESBL-resistant infections, in contrast to these findings, these were found to be associated with mortality in our study.[6,20,26] Short-term use or, if possible, not using indwelling catheters is important to control infection and reduce mortality.

In our study, the duration of treatment was longer in the ESBL-producing group and the use of carbaphem in treatment was significantly higher. Identifying and correcting the factors that increase ESBL resistance may help shorten treatment duration and prevent unnecessary carbaphem use.

In addition, our results showed that mortality was lower in those using cephalosporins and higher in those using colistin. The use of β-lactam-β-lactamase inhibitor combinations in the treatment of the ESBL-non-producing group was more frequent in our study. The use of narrow-spectrum antibiotics as much as possible is important to reduce antibiotic resistance rates and mortality.

This study had several limitations. First, due to the retrospective design, data were obtained from clinical reports, so some incomplete data were inevitable. According to the literature, the number of patients in our study was high compared with single-center studies. However, this was a single-center study. Multicenter studies can help clarify demographic and epidemiologic characteristics and avoid statistical limitations. The data also lack genotyping and molecular analysis, which, if available, would be very valuable in demonstrating.

Conclusion

Klebsiella spp. is one of the major causes of health care-associated BSI infections in pediatric patients. We found that younger age, neurometabolic disease, prior use of antibiotics, especially aminoglycosides, β-lactam-β-lactamase inhibitor combinations, and cephalosporins in the last 30 days, and being in an intensive care unit were strongly associated with the development of BSI with ESBL-producing *Klebsiella spp.* Mortality was higher in patients with CRBSI, presence of central venous and urinary catheters, mechanical ventilation, intensive care unit patients, history of carbapenem, aminoglycoside, and fluoroquinolone use in the previous 30 days, treatment with colistin, thrombocytopenia, and elevated CRP. It is clear that some of these factors may be preventable. These results suggest that the appropriate choice of antimicrobial agents, less invasive procedures may reduce the incidence of BSIs caused by *Klebsiella spp*., especially ESBL-producing *Klebsiella* in children. The use of narrow-spectrum antibiotics and as few antibiotics as possible is important to reduce ESBL resistance and mortality.

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Ankara City Hospital Ethic Commitee (decision no: E2-23-4168, date: 26.05.2023).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

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