JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Pediatric Gram-negative bloodstream infections: epidemiology, antibiotic resistance, clinical outcomes and factors affecting mortality, a single center retrospective study

Seyhan Yilmaz[1], Gulsen Akkoc[1], Sevgi Aslan Tuncay[1], Burcu Parlak[1], Pinar Canizli Erdemli[1], Aylin Dizi Isik[1], Zeynep Ergenc[1], Arzu Ilki[2], Nurver Ulger Toprak[2], Bilgehan Ergan[2], Sevliya Ocal Demir[1], Eda Kepenekli[3]

[1] *Marmara University School of Medicine, Pediatric Infectious Disease, Istanbul, Turkey*
[2] *Marmara University Faculty of Medicine, Medical Microbiology, Istanbul, Turkey*
[3] *Bahcesehir University Faculty of Medicine Goztepe Medical Park Hospital, Pediatric Infectious Disease, Istanbul, Turkey*

Abstract

Introduction: The increasing prevalence of Gram-negative bloodstream infections in pediatric patients poses significant treatment challenges, particularly from multi-drug resistant (MDR) strains. Despite advances in medical care, mortality from bloodstream infections remains a concern. Our study aims to understand pediatric patients' demographics, clinical conditions, and microorganisms causing Gram-negative infections, as well as identify factors affecting treatment outcomes and mortality.

Methodology: A retrospective, observational study of Gram-negative bacteremia, including all patients < 18 years of age, hospitalized during 2022, with documented bacteremia caused by *Enterobacteriaceae* or non-fermentative bacteria.

Results: In total 123 blood cultures from 102 patients were included study. The median age of patients was 22 months, with 85.3% having an underlying medical condition. Common strains were *Klebsiella pneumoniae, Escherichia coli,* and *Pseudomonas aeruginosa*, with 73.2% hospital-acquired infections. Among the isolated species, 28.5% were multidrug-resistant (MDR). The mortality rate was 10.5%. Mortality among patients with antibiotic-resistant isolates was 17.1%. Patients with sepsis had a markedly elevated mortality rate. Additionally, mortality was increased among patients reliant on mechanical ventilation and those with urinary catheters. Furthermore, central venous catheterization was found to be an independent predictor for sepsis (odds ratio: 2.463, 95% confidence interval: 1.095–5.53), while the presence of a urinary catheter was identified as an independent predictor of mortality (odds ratio: 5.681, 95% confidence interval: 1.142–28.249).

Conclusions: The study findings highlight a critical need for strategies to reduce MDR Gram-negative infections in children, emphasizing the importance of timely removal of invasive devices and rational antibiotic use to improve patient outcomes.

Key words: Gram-negative bacteremia; multi-drug resistance; pediatric bacteremia; pediatric sepsis.

J Infect Dev Ctries 2025; 19(2):238-247. doi:10.3855/jidc.20258

(Received 20 April 2024 – Accepted 03 October 2024)

Introduction

Bloodstream infections (BSIs), also known as bacteremia, are critical medical conditions causing sepsis, septic shock, or death [1]. Mortality is affected by multiple factors such as causative pathogens, early diagnosis, and effective treatment. Mortality associated with pediatric bloodstream infections remains a concern, although advanced medical care [2].

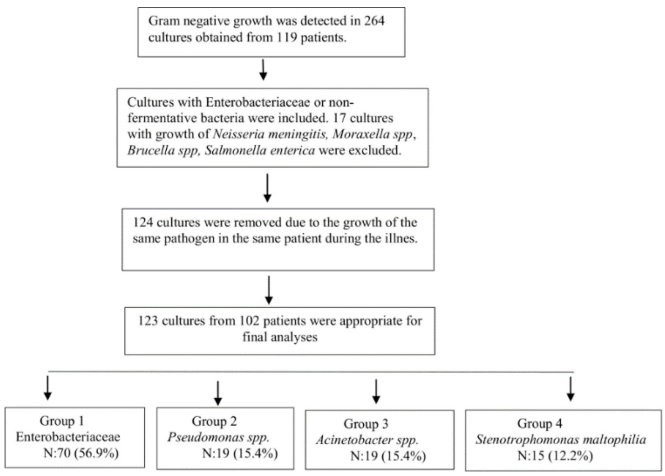
The incidence of Gram-negative organisms causing BSI has increased over the years. In developing countries, Sajedi Moghaddam *et al.* (2024) conducted a study in an Iranian referral hospital, which revealed that 54% of pediatric bloodstream infections were caused by Gram-negative bacteria. The most commonly isolated organisms were *Pseudomonas spp.* (17.6%) and *Klebsiella pneumoniae* [3]. Similarly, Trehan *et al.* (2014) studied invasive bacterial infections in a pediatric oncology unit in India and found that Gram-negative organisms accounted for 56% of the cases, with *Escherichia coli* and *Klebsiella pneumoniae* being the most frequent pathogens [4]. In contrast, in developed countries, Folgori *et al.* (2014) reported that 26% of bloodstream infections in a European tertiary pediatric hospital were caused by Gram-negative bacteria [5]. Moreover, Armenian *et al.* (2005) found that in a pediatric intensive care unit in the U.S., Gram-positive and Gram-negative organisms accounted for 72.7% and 22.7% of total isolates, respectively [6]. These findings highlight that in developing countries, Gram-negative infections tend to be more prevalent and

are often associated with significant morbidity and mortality. In developed countries, although Gram-positive bacteria are more commonly isolated, Gram-negative pathogens continue to pose a serious threat in pediatric bloodstream infections.

Gram-negative bacteria may exhibit multidrug resistance [7,8]. Multi-drug resistance is a growing issue in pediatric patients, leading to increased morbidity, mortality, and prolonged hospitalization [9,10]. Aizawa *et al.* (2019) conducted a study in children's hospitals in Japan from 2010 to 2017, which showed that 24.5% of Gram-negative bloodstream infections (BSIs) were caused by multidrug-resistant organisms [11]. Similarly, Ivady *et al.* (2016) found that 31% of Gram-negative isolates in pediatric bloodstream infections exhibited multidrug resistance [12]. *Enterobacteriaceae* especially *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter spp.,* and non-lactose fermenting bacteria such as *Pseudomonas aeruginosa* or *Acinetobacter spp.* have been identified as major causes of multi-drug resistant Gram-negative bloodstream bacterial infections [13-15]. Resistant Gram-negative bacterial pathogens cause severe infections, especially in high-risk patients hospitalized in pediatric intensive care units, hematology-oncology clinics, and transplantation centers. Additionally, the extensive use of invasive medical devices, immunosuppressive therapies, and frequent hospitalization facilitate the acquisition of infections. The limited choice of effective treatment options makes them a significant treatment and infection control challenge [16-18].

Studies evaluating the risk factors increasing mortality and effective treatment options in resistant Gram-negative infections in children are limited. Previous studies have mostly focussed on the adult population. Some studies are limited to specific age groups or specific pathogens in pediatric patients [19-21]. Few studies have been conducted on the clinical outcomes of Gram-negative bloodstream infections in pediatric patients [20,22,23]. Pediatric patients, especially those with underlying medical conditions, immunodeficiency, malignancy, or intensive care requirements, are at high risk for Gram-negative bloodstream infections [24]. To improve clinical outcomes in pediatric patients with Gram-negative infections, we must close the current knowledge gap and prioritize pediatric-centered research. The primary aim of our study was to evaluate the demographic and clinical characteristics of patients, the causative organisms, and resistance patterns in Gram-negative BSIs in children. The other aims of our study include determining the factors affecting clinical outcomes and mortality.

Figure 1. Study flow chart.



Methodology

Setting and patients

In this retrospective study, pediatric patients aged 0-18 years with Gram-negative bacteria growth in blood cultures were investigated in a tertiary hospital over a one-year period. We included cultures with growth *Enterobacteriaceae* or non-fermentative bacteria in the analysis. Cultures with growth of *Neisseria meningitidis*, *Moraxella spp*., *Brucella spp*., and *Salmonella enterica* were excluded as these pathogens were outside the scope of the study. Additionally, cultures showing the growth of the same pathogen from the same patient within one month were excluded to avoid duplication. The diagram of the study is shown in Figure 1.

Data collections

Age, gender, department of hospitalization, underlying diseases, duration of hospital stay, history of parenteral or oral antibiotic use, 30-day history of corticosteroid or chemotherapeutic drug use, immunodeficiency status (primary, secondary), surgical operations, administration of hemodialysis, use of a mechanic ventilator and central venous catheter were recorded. In addition, the peripheral leukocyte count, platelet count, and C-reactive protein (CRP) levels that were assessed on the day when the positive blood culture was obtained and CRP at the end of treatment were recorded. The clinical presentations of the patients and sepsis development were noted.

Definitions

Bacteremia is the presence of bacteria in the blood as evidenced by a positive blood culture. Sepsis was defined by the International Pediatric Sepsis Consensus Conference sepsis guideline in 2005 [25]. Infections that occurred 48 hours after hospital admission to hospital were considered hospital-acquired infections [26].

A polymicrobial BSI is defined as the growth of multiple microorganisms in a blood culture, except coagulase-negative staphylococci, *Corynebacterium spp*., and *Propionibacterium spp.* If one of these latter three microorganisms is detected in a blood culture alongside Gram-negative bacilli, it is considered to be a result of skin contamination rather than a polymicrobial BSI.

The definition of antibiotic-resistant strains is classified as multidrug-resistant (MDR), extensively drug-resistant, or pan-drug-resistant as defined by Magiorakos *et al.* [27]. We grouped extensively drug-resistant bacteria and pan-drug-resistant bacteria as MDR to simplify the analysis.

Microbiologic Methods

Blood culture specimens were inoculated into a blood culture bottle (Bact/Alert RF Plus Biomerieux, France). They were incubated at 35 °C in BACT/ALERT Blood Culture System cabinets for 5 days. Clinical isolates were identified by VITEK MS PRIME (Biomeriux, France).

Susceptibility to antimicrobial agents was determined by the standard disc diffusion method. Antimicrobial susceptibility tests were confirmed by determination of minimal inhibitory concentrations (MICs) by microdilution method. Antibiotic susceptibility results were performed and interpreted according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical Analysis

Demographic and descriptive continuous variables with normal distribution are reported as mean (standard deviation, SD), whereas non-normally distributed data are presented as median values (interquartile range, IQR). Categorical variables are expressed as percentages. The chi-square test was used to compare categorical variables. Median or mean values between the two groups were compared using the Mann-Whitney U test whether Student's t-test depended on the sample distribution. A p value of ≤ 0.05 were considered statistically significant. The possible factors found in the univariate analysis were entered into a logistic regression analysis The odds ratio and confidence intervals were calculated to assess independent predictors of sepsis and mortality in the multivariate analysis. The data of the patients were analyzed with IBM SPSS Statistics 26.0.

Ethics statement

A written informed consent form was obtained from the parents of the cases. The ethics committee approval was obtained from the Marmara University Faculty of Medicine Research Ethics Committee on June 5, 2023, with the approval number 09.2023.620.

Results

Patients and settings

Gram-negative growth was detected in 264 cultures obtained from 119 patients between 1 January and 31 December 2022. Finally, 123 BSI episodes taken 102 patients were analyzed. We excluded 17 cultures with the growth of *Neisseria meningitis, Moraxella spp*, *Brucella spp,* and *Salmonella enterica*. 124 cultures were removed due to the growth of the same pathogen in the same patient within one month. The median age of patients was 22 months (interquartile range: 6-74 months). Seventy-eight of 123 BSI cases were taken from females (63.4%). Most children (105 of 123 cases; 85.3%) had at least one underlying illness; the most common were solid tumor (n = 19, 15.4%), primary immune deficiency (n = 13, 10.5%), cerebral palsy (n = 12, 9.8%), acute lymphoblastic leukemia (n = 9, 7.3%) respectively. There was primary immunodeficiency in

Table 1. Demographic and clinical characteristics of patients.

Demographic features	**n (%), (n = 123)**	
Female	78 (63.4)	
Male	45 (36.6)	
Median Age (months)	22 (IQR:6-74)	
Age group		
0-12 months	46 (37.4)	
13-60 months	39 (31.7)	
> 60 months	38 (30.9)	
Clinical features		
Pediatric ward	60 (48.8)	
Pediatric intensive care unit	43 (35)	
Hematology oncology	20 (16.3)	
	No	**Yes**
Antibiotherapy	16 (13)	107 (87)
Chemotherapy	94 (76.4)	29 (23.6)
Hemodialysis	118 (95.9)	5 (4)
Mechanical ventilation	86 (69.9)	37 (30.1)
Central venous catheter	45 (36.6)	78 (63.4)
Operation	85 (69.1)	38 (30.9)
Clinical outcome		
Sepsis	51 (41.5)	
Bacteremia	72 (58.5)	
Death	13 (10.6)	
Discharge	22 (17.9)	
Still hospitalized	88 (71.5)	

IQR: Interquartile range.

13 (10.6%), secondary immunodeficiency in 28 (22.8%) cases. Eighty-two (66.7%) of the cases were not immunocompromised. The clinical and demographic characteristics of the patients are shown in Table 1.

Thirty-three cases (26.8) of the BSIs were community-acquired, and 90 (73.2%) were hospital-acquired (HA) infections. Gram-negative growth was detected on average 13 days after hospitalization (IQP 2-55 days). In 39 (31.7%) of BSIs, the infection was catheter-associated bloodstream infection.

Causative microorganisms, antimicrobial resistance, and risk factors for multidrug resistance

In this study, 123 cultures, with 18 polymicrobial and 105 monomicrobial BSIs, were analyzed. The microorganism groups isolated are shown in Figure 1. The most frequently isolated relevant Gram-negative microorganisms were *K. pneumoniae* (18.7%), *E. coli* (15.4%), and *P. aeruginosa* (11.4%). The causative organisms in Gram-negative culture growth are shown in Supplementary Table 1.

Antibiotic resistance patterns of microorganisms are presented in Table 2. In all groups, ceftriaxone resistance was 25%. *K. pneumonia* in the *Enterobacteriaceae* had the highest resistance to ceftriaxone and ceftazidime. Carbapenem resistance was highest in the *P. aeruginosa* (28,5%). Carbapenem resistance was 5.7% in *Enterobacteriaceae* and 5.3% in *Acinetobacter spp.* respectively. Among community-acquired *Enterobacteriaceae* (n: 19) infections, no strains were found to be carbapenem-resistant. However, carbapenem resistance was observed in 20% (n: 1/5) of community-acquired *Pseudomonas spp*. isolates and 12.5% (n: 1/8) of *Acinetobacter spp*. isolates, respectively. The rate of MDR isolates among all isolates was 35 (28.5%). A difference was detected between the groups. *Enterobacteriaceae* had the highest frequency 33 (94.3%) ($p < 0.001$) compared to other groups.

The MDR rate was higher among patients hospitalized in the intensive care unit compared to patients admitted to non-PICU departments ($p = 0.019$). While there is no statistical significance, the MDR group exhibited higher rates of antibiotic exposure, secondary immunodeficiency, chronic diseases, mechanical ventilator dependency, and chemotherapy exposure compared to the non-MDR group. Furthermore, the median leukocyte count was lower in the MDR group compared to the non-MDR group ($p = 0.034$). Similarly, the mean polymorphonuclear cell count was lower in the MDR group compared to the non-MDR group ($p = 0.043$) (Table 3).

Thirty-eight patients (30.9%) underwent surgery within the last 30 days. The most common procedures were tumor resection in nine patients, ventriculoperitoneal shunt placement in six patients, and port catheter placement in five patients. Among these patients, 12 (34.3%) developed multidrug-resistant (MDR) Gram-negative infections. No significant association was found between undergoing surgery and the development of MDR Gram-negative infections.

Clinical Outcome Data and Risk Factors

Fifty-one patients (41.4%) had a clinical presentation of sepsis. Among those who developed sepsis, female gender was more common [n: 38 (74%); $p = 0.032$]. The rate of having a chronic disease was higher in patients with sepsis (90%) compared to those without sepsis (81.9%) but was not statistically significant ($p = 0.217$). The rate of mechanical ventilator dependency, presence of a urinary catheter, chemotherapy, steroid exposure, intensive care unit requirement, and surgery were higher in patients with

Table 2. In vitro resistance of Gram-negative pathogens to frequently used antimicrobial agents (expressed in absolute numbers; percentages is brackets).

Antimicrobial agent	AMX-C	CXM	CTX	CFD	CFP	MEM	PIP-T	GEN	AMI	CIP	TRI-S
All pathogens (n:123)	47 (38.2)	33 (26.8)	25 (20.3)	30 (24.4)	24 (19.5)	9 (7.3)	23 (18.7)	15 (12.2)	8 (6.5)	22 (17.9)	28 (22.8)
Enterobacteriaceae (*n* :70)	47 (67.1)	33 (47.1)	25 (35.7)	26 (37.1)	24 (34.2)	4 (5.7)	22 (31.4)	13 (18.5)	6 (8.5)	20 (28.5)	25 (35.7)
Klebsiella spp (n:28)	15 (53.5)	19 (67.8)	15 (53.5)	15 (53.5)	12 (42.8)	3 (10.7)	10 (35.7)	5 (17.8)	4 (14.2)	6 (21.4)	9 (32.1)
Escherichia coli (n:19)	13 (68.4)	14 (73.6)	9 (47.3)	9 (47.3)	11 (57.8)	1 (5.2)	10 (52.6)	8 (42.1)	2 (10.5)	14 (73.6)	15 (78.9)
Enterobacter spp (n:11)	10 (90.9)	NA	1 (9)	2 (18.1)	1 (9)	0	2 (18.1)	0	0	0	0
Serratia spp (n:11)	9 (81.8)	NA	0	0	0	0	0	0	0	0	0
Proteus mirabilis (n:1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (100)
Non-enterobacteriaceae (n:53)	NA	NA	NA	NA	NA	5 (9.4)	1 (1.8)	2 (3.7)	2 (3.7)	2 (3.7)	3 (5.6)
Pseudomonas spp (n:19)	NA	NA	NA	0	0	4 (21)	1 (5.2)	0	0	1 (5.2)	NA
Pseudomonas aeruginosa (n:14)	NA	NA	NA	1 (7.1)	0	4 (28.5)	1 (7.1)	0	0	1 (7.1)	NA
Acinetobacter spp (n:19)	NA	NA	NA	3 (15.7)	NA	1 (5.2)	NA	2 (10.5)	2 (10.5)	1 (5.2)	2 (10.5)
Stenotrophomonas maltophilia (n:15)	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	1 (6.6)

AMI: Amikacin; AMX-C: Amoxicillin–clavulanic acid; CFD: Ceftazidime; CFP: Cefepime; CIP: Ciprofloxacin; CTX: Cefriaxone; CXM: Cefuroxime (axetil or sodium); GEN: Gentamicin; MEM: Meropenem; TRI-S: Trimethoprim–sulfamethoxazole; PIP-T: Piperacillin–tazobactam; NA: not available.

sepsis than in patients without sepsis, but not statistically significant (Table 3).

The median platelet count was lower in patients with sepsis than in those without sepsis ($p < 0.001$). The median CRP value was higher in patients with sepsis than in those without sepsis ($p = 0.008$). In addition, the median CRP value at the end of treatment was higher in patients with sepsis than in patients without sepsis ($p < 0.001$) (Table 3).

The 30-day mortality rate was 10.5% (n: 13). The cause of death was sepsis in 92% (n: 12) of cases. Female gender was more common at 98.2% (n: 12) in patients with exitus ($p = 0.03$). The median age of patients who died was higher than those who survived ($p = 0.042$). In six patients, culture sterilization was not achieved. *E. coli* growth was detected in five, *K. pneumonia* in three, *P. aeruginosa* in two, *Serratia marcenses* in two, and *Stenotrophomonas maltophilia* in one of the exitus patients. The one-year mortality rate was 22.7% (n: 28). The cause was sepsis in 67.8% (n: 19).

The rate of exitus was higher in patients with sepsis than without sepsis (19.6% vs 4.2%; $p = 0.008$). The exitus rate was higher in the group with MDR growth (17.1%) compared to the group without MDR growth (8%) ($p = 0.135$), but this result was not statistically significant. In patients who died the rate of presence of urinary catheters (69.2%) was higher than in survivors (28.2%) ($p = 0.005$). The rate of mechanical ventilator dependence was higher in patients who died than in survivors (61.5% vs 26.4%; $p = 0.021$). Despite lacking statistical significance, patients who did not survive showed a higher incidence of central venous catheter use, chemotherapy, and steroid exposure compared to those who survived.

The median leukocyte count was lower in the patients were died than survivors but it was not statistically significant ($p = 0.225$). Similarly, the median platelet count was lower in patients were died than survivors ($p < 0.001$). The median CRP value was higher in patients were died than in survivors ($p < 0.001$). Furthermore, the median CRP value at the end of treatment was higher in patients with exitus than in patients with survivors ($p < 0.001$) (Table 3).

When compared according to the duration to obtain sterile culture, it was observed that sterile culture was obtained longer in patients with a central venous catheter, urinary catheter, and non-survivors (*p* values: 0.026, 0.020, and 0.021 respectively). No significant data were found in other variables.

For predicting sepsis, a multivariate logistic regression model, which was based on demographic features, age, gender, antibiotherapy, chemotherapy, mechanic ventilation, and central venous catheter, revealed that central venous catheter was independent predictors of sepsis with an odds ratio of 2.463 (95% CI: 1.095–5.53). Factors affecting the mortality rate were analyzed by multivariant logistic regression model and revealed that urinary catheter was an independent factor in mortality rate with an odds ratio of 5.681(95% CI: 1.142–28.249).

The treatment regimens and mean duration of treatment according to the results of strain and antimicrobial susceptibility of the patients are shown in

Table 3. Risk factors for clinical outcome and multi-drug resistance.

	MDR (+) N (%)	MDR (-) N (%)	*p*	Sepsis (+)	Sepsis (-)	*p*	Exitus	Survival	*p*
Female	23 (65.7)	55 (62.5)	0.738	38 (74)	40 (55)	**0.032**	12 (92.8)	66 (60)	**0.03**
Male	12 (34.3)	33 (37.5)		13 (25)	32 (44)		1 (7.7)	44 (40)	
Age (months)	23 (9.5-93)	17.5 (6-73.2)	0.567	23 (7-73)	20 (6-85.8)	0.560	35 (13.5-174.5)	18.5 (6-73)	**0.042**
Enterobacteriaceae	33 (94.3)	37 (42)	**< 0.001**	35 (68)	35 (48)	0.105	10 (76.9)	60 (54.5)	0.319
Pseudomonas spp	1 (2.9)	18 (20.5)		6 (11.8)	13 (18.1)		2 (15.4)	17 (15.5)	
Acinetobacter spp	1 (2.9)	18 (20.5)		4 (7.8)	15 (20.8)		0 (0)	19 (17.3)	
Stenotrophomonas maltophilia	0	15 (17)		6 (11.8)	9 (12.5)		1 (7.7)	14 (12.7)	
With CVC	24 (68.6)	54 (61.4)	0.454	39 (76.5)	39 (54.2)	**0.011**	11 (84.6)	67 (60.9)	0.13
With urinary catheter	14 (40)	26 (29.5)	0.264	20 (39.2)	20 (27.8)	0.182	9 (69.2)	31 (28.2)	**0.005**
Connected to MV	12 (34.3)	25 (28.4)	0.521	17 (33.3)	20 (27.8)	0.508	8 (61.5)	29 (26.4)	**0.021**
Sepsis	14 (40)	37 (42)	0.835						
ICU	14 (40)	29 (33)	0.46	23 (45.1)	20 (27.8)	**0.047**	5 (11.6)	38 (88.4)	0.767
Exitus	6 (17.1)	7 (8)	0.135	10 (19.6)	3 (4.2)	**0.008**			
Day of hospitalisation when the culture was obtained	13 (1-48)	13.5 (2.2-59.7)	0.56	22 (2-62)	11 (2-38.7)	0.101	53 (5-80.5)	12.5 (2-46.5)	0.174
Day of culture negative	2 (1-2.5)	2 (1-2.5)	0.7	2 (1-3)	2 (1-2)	0.67	2 (1-2.75)	2 (1-2.25)	0.946
Leucocyte count (WBC) $10^3/\mu L < 4000$	8600 (400-13400)	10050 (5600-17225)	**0.034**	8400 (2600-14000)	10200 (5600-15550)	0.34	1900 (200-13050)	9600 (5600-15775)	**0.0068**
Polymorphonuclear (PMN) cell count $10^3/\mu L < 500$	4100 (0-8300)	5150 (2500-11725)	**0.043**	5000 (900-11900)	5400 (2475-8775)	0.992	1500 (0-11650)	5300 (2300-9000)	0.225
Platelet count $10^3/\mu L$	75000 (16000-332000)	154000 (74250-372250)	0.073	98000 (22000-207000)	207000 (79500-392750)	**< 0.001**	16000 (3500-85000)	163500 (69000-336000)	**< 0.001**
C- reactive protein (CRP) mg/L	119 (50.5-192.7)	74 (37-147.5)	0.185	127.5 (57-190.5)	68 (24.5-137.5)	**0.008**	211 (154-344)	68 (37-139)	**< 0.001**

CVC: Central venous catheter, MV: mechanical ventilator, ICU:Intensive care unit.

Table 4. The treatment regimens of the patients who did not survive are shown in Supplementary Table 2. Exitus was not observed in meropenem/aminoglycoside, meropenem/colistin, ertapenem/meropenem/colistin combination therapies, or ceftazidime avibactam treatment regimens.

Discussion

Our study, in which we collected data for 12-months in our tertiary referral hospital, represents one of the very few cohort studies in which Gram-negative growths in pediatric patients have been analyzed. The study included children from all age groups and several departments with different specialties including neonatal and pediatric intensive care, pediatric surgical intensive care, hematology–oncology, and stem cell transplantation. The main foci of our study were etiologic agents of pediatric GNB-BSI and factors that influence multidrug resistance and outcome.

In our study, the predominant isolates were *K. pneumoniae, E. coli*, and *P. aeruginosa.* The frequency of causative organisms varies according to the age, ward, and underlying disease of the patients. When studies conducted in pediatric and adult populations are examined, *E. coli* and *Klebsiella spp* are the most common organisms of Gram-negative infections in all groups [28-33].

In this current study, the MDR rate was found to be 28.5% (n: 35) among all isolates. This rate was lower compared to adult studies [34,35]. In the literature, while many studies focus on specific patient groups or pathogens, there's a lack of research providing MDR rates in broad pediatric populations. Studies like Ivady *et al.* and Folgori *et al.* reported higher MDR rates (33.6% and 39% respectively) compared to our findings [5,12]. However, a Japanese study reported a similar rate to ours (24.5%) [36]. The variation in rates may arise from differing MDR definitions and how resistance is categorized. Additionally, factors like location, antimicrobial use, infection control practices, and patient demographics can influence MDR rates across settings.

In our study, *Enterobacteriaceae* had the highest frequency compared to other groups. The strains with the highest MDR rate were *K. pneumonia* and *E. coli.* This finding is consistent with previous studies [12]. A likely explanation for the predominance of *Enterobacteriaceae* in our study cohort is the presence of predisposing factors that may indicate their increased passage through the intestinal barrier within our study population. Factors such as antibiotic use, immunosuppression, prolonged hospitalization, and severe underlying illnesses, which are prevalent among our patients may be potential enhancers of the translocation of *Enterobacteriaceae* across the intestinal mucosa. Additionally, in our study, carbapenem resistance was found in hospital-acquired *Enterobacteriaceae*, while community-acquired strains showed no resistance. These findings align with prior research on carbapenem-resistant *Enterobacteriaceae* (CRE) infections [37]. Our results emphasize the

Table 4. The treatment regimens and mean duration of treatment according to the results of strain and antimicrobial susceptibility of the patients are shown; patient number (mean duration of treatment in brackets).

	SAM	SAM + GEN	CTX	CFD	CFP	PIP-T	MEM	MEM + GEN	MEM + AMI	MEM + COL	ETP + MEM + COL	CIP	CIPRO + TRI-S	CFD-AVI	CFD-AMI	CTX-GEN
A. baumannii	-	1 (14)	-	-	-	-	2 (14)	1 (14)	1 (13)	1 (57)	-	-	-	-	-	-
A. haemolyticus	-	-	-	-	-	-	1 (10)	-	-	-	-	-	-	-	-	-
A. lwoffii	1 (7)	-	-	1 (7)	-	-	2 (5)	-	2 (15)	1 (15)	-	-	-	-	-	-
A. pittii	-	-	-	-	-	-	1 (14)	-	-	1 (14)	-	-	-	-	-	-
A. radioresistens	-	-	1 (7)	-	-	-	-	-	-	-	-	-	-	-	-	-
A. ursingii	-	-	-	-	-	-	1 (14)	-	-	1 (16)	-	-	-	-	-	-
E. aerogenes	-	-	-	-	-	-	2 (10)	1 (14)	-	-	-	-	-	-	-	-
E. cloacae complex	-	-	-	1 (10)	-	-	3 (13)	-	2 (14)	1 (19)	-	-	-	-	-	-
E. hormaechei	-	-	-	-	-	-	1 (14)	-	-	-	-	-	-	-	-	-
E. coli	-	-	2 (5)	-	1 (7)	1 (1)	15 (13)	-	-	-	-	-	-	-	-	-
K. oxytoca	-	-	2 (8)	-	-	-	2 (12)	-	-	1 (7)	-	-	-	-	-	-
K. pneumoniae	-	-	2 (6)	1 (10)	1 (10)	-	10 (10)	1 (14)	2 (15)	1 (14)	1 (15)	1 (10)	-	4 (12)	-	-
Proteus mirabilis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1 (14)
P. aeruginosa	-	-	-	-	-	-	7 (13)	-	4 (10)	2 (13)	-	-	-	-	1 (8)	-
P. oryzihabitans	1 (8)	-	-	-	-	-	-	-	1 (11)	-	-	-	-	-	-	-
P. putida	-	-	-	-	-	-	1 (20)	-	-	-	-	-	-	-	-	-
P. stutzeri	-	-	-	-	-	-	-	-	1 (14)	1 (14)	-	-	-	-	-	-
S. liquefaciens	-	-	-	-	-	-	1 (20)	-	-	-	-	-	-	-	-	-
S. marcescens	-	-	1 (10)	-	1 (14)	1 (7)	6 (9)	-	1 (7)	-	-	-	-	-	-	-
S. maltophilia	-	-	-	-	-	-	-	-	-	-	-	2 (14)	12 (10)	1 (13)	-	-

AMI: Amikacin; CFD: Ceftazidime; CFD-AVI: Ceftazidime-avibactam; CIP: Ciprofloxacin; CTX: Cefriaxone; COL: Colistin; ETP: Ertapenem; CFP: Cefepime; GEN: Gentamicin; MEM: Meropenem; PIP-T: Piperacillin–tazobactam; SAM:Ampicillin-sulbactam; TRI-S: Trimethoprim–sulfamethoxazole.

necessity of proper antibiotic strategies and infection control measures in hospitalized patients.

In our study, the mortality rate was higher in patients with MDR organisms (17.1%) than in non-MDR cases (8%), but it was not statistically significant ($p = 0.135$). In line with our study, Tsai *et al.* revealed 11% to 29% case fatality depending on non- MDR or MDR infections [28]. The literature shows that mortality is higher in the MDR group compared to the non-MDR group highlighting the significance of MDR growths on mortality in pediatric patients [28,34]. Our findings reveal that a comprehensive approach is needed to reduce the spread of resistant microorganisms in children. This approach includes promoting antibiotic stewardship, implementing infection control measures such as rigorous hand hygiene and isolation protocols for infected patients, conducting regular surveillance for resistant strains, raising awareness about antibiotic resistance, and investing in the development of new treatments. These collective efforts aim for early intervention and the reduction of mortality rates in children.

In our cohort study, the rate of hospital-associated bloodstream infection was found to be 73.1%. This rate was higher than the rates reported in the literature by Levy *et al.* (47%) and Al Hasan *et al.* (60%) [22,23]. This high rate may be explained by the prevalence of chronic diseases among our patients and the high number of patients requiring intensive care. Most children in this cohort (n: 105, 85.3%) had underlying medical conditions predisposing to Gram-negative BSI, which is consistent with the results of previous reports such as those by Folgori *et al.* (84.9%) and Ivady *et al.* (92.5%) [5,12].

In our study, fifty-one patients (41.4%) had a clinical presentation of sepsis. The presence of a central venous catheter (CVC) was found to be an independent risk factor for sepsis. The extended duration time of CVCs creates an environment conducive to microbial colonization [38]. Gram-negative bacteria developing in biofilms on catheter surfaces increase the risk of bloodstream infection during catheter-related procedures [39,40]. The presence of CVCs amplifies the clinical implications of Gram-negative bacteremia, making patients more susceptible to severe sepsis [41,42]. This finding of our study underscores the significance of timely catheter removal when deemed unnecessary, to prevent long-term exposure to Gram-negative pathogens.

The mortality rate was 10.5%, sepsis-related mortality was 9.7% in our study, Mortality rate ranged between 11% and 17% in previous studies [5,22]. Sepsis was identified as an independent risk factor for mortality in the current study, consistent with findings in the literature [12]. In our cohort, mortality was higher among patients reliant on mechanical ventilation and those with urinary catheterization. Previous studies have similarly revealed that increase in mechanical ventilator use in non-survivors [41]. Moreover, indwelling urinary catheters have been implicated as potential sites for bacteremia due to their role in bacterial proliferation. Existing literature suggests that urinary catheters can lead to health care-associated infections (HCAIs) with catheterized patients exhibiting a high incidence of sepsis [42].

Our study revealed that sterile cultures were achieved later in patients with central venous catheters, urinary catheters, and non-survivors. These catheters pose a risk of bloodstream pathogen transmission and subsequent bacteremia [38-40]. Our study's findings underscore the necessity of removing invasive devices when they are no longer medically necessary.

Our study has several important limitations. First, the retrospective design introduces inherent constraints on data collection and accuracy, as it relies on previously recorded information rather than prospectively gathered data. This may have resulted in variability in data completeness and quality.

Second, this study was conducted at a single medical center, which limits the generalizability of our findings to broader patient populations or other healthcare settings. The practices and resources specific to our institution may not reflect those in other regions, thereby limiting the applicability of our results.

Third, blood cultures were obtained at irregular intervals due to the retrospective nature of the study. This inconsistency may have introduced variation in the detection of bloodstream infections (BSIs) and the assessment of their causative organisms. Unfortunately, this information was not readily available in many patient records, further limiting our ability to draw conclusions in this area.

Lastly, incomplete data availability for some patients adds another layer of complexity. Missing information on critical variables such as treatment details, microbiological findings, and clinical outcomes may have affected our analysis and interpretation of the results. This could potentially lead to bias or imprecision in estimating the true association between bloodstream infections, MDR pathogens, and patient outcomes

Conclusions

MDR pathogens caused one-quarter of Gram-negative BSI cases, posing a significant threat to children with underlying diseases due to limited treatment options and higher mortality rates. Strategies such as rational antibiotic use and timely removal of invasive devices are crucial for reducing MDR infections. Our study helps fill the gap in research on pediatric risk factors and outcomes, contributing to the development of effective interventions.

Authors' contributions

Contributors SY was responsible for the organisation and coordination of the study. GA is the principal investigator and was responsible for data analysis. SAT was responsible for data collection and literature search. ZE , ADI, BP, and PCE were responsible for data collection and data processing. AI, NU and BE were responsible for study design, data collection, and interpretation of data. EK and SOD were responsible for study design, organisation of the study, and final review. All authors read and approved the final manuscript.

Corresponding Author

Eda Kepenekli
23 Nisan Street, Bahcesehir University Faculty of Medicine Goztepe Medical Park Hospital,
Faculty of Medicine No. 17, 34732 Kadiköy, Istanbul, Turkey
Tel: +90 (216) 468-4444
Fax: +90 216 625 45 45
E-mail: ekepenekli@yahoo.com

Conflict of interests

No conflict of interests is declared.

References

1. Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M (2010) Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003-2005. Pediatr Infect Dis J 29: 310-313. doi: 10.1097/INF.0b013e3181d73322.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41: 580-637. doi: 10.1097/CCM.0b013e31827e83af.
3. Sajedi Moghaddam S, Mamishi S, Pourakbari B, Mahmoudi S (2024) Bacterial etiology and antimicrobial resistance pattern of pediatric bloodstream infections: a 5-year experience in an Iranian referral hospital. BMC Infect Dis 24: 373. doi: 10.1186/s12879-024-09260-w.
4. Trehan A, Totadri S, Gautam V, Bansal D, Ray P (2014) Invasive bacterial infections in a pediatric oncology unit in a tertiary care center. Indian J Cancer 51: 428–431. doi: 10.4103/0019-509X.175368.
5. Folgori L, Livadiotti S, Carletti M, Bielicki J, Pontrelli G, Ciofi Degli Atti ML, Bertaina C, Lucignano B, Ranno S, Carretto E, Muraca M, Sharland M, Bernaschi P (2014) Epidemiology and clinical outcomes of multidrug-resistant, Gram-negative bloodstream infections in a European tertiary pediatric hospital during a 12-month period. Pediatr Infect Dis J 33: 929-32. doi: 10.1097/INF.0000000000000339.
6. Armenian SH, Singh J, Arrieta AC (2005) Risk factors for mortality resulting from bloodstream infections in a pediatric intensive care unit. Pediatr Infect Dis J 24: 309–314. doi: 10.1097/01.inf.0000157086.97503.bd.
7. Luzzaro F, Ortisi G, Larosa M, Drago M, Brigante G, Gesu G (2011) Prevalence and epidemiology of microbial pathogens causing bloodstream infections: results of the OASIS multicenter study Diagn Microbiol Infect Dis 69: 363-9. doi: 10.1016/j.diagmicrobio.2010.10.016
8. Muñoz P, Cruz AF, Rodríguez-Créixems M, Bouza E (2008) Gram-negative bloodstream infections. Int J Antimicrob Agents 32: S10–S14. doi: 10.1016/j.ijantimicag.2008.06.015.
9. Antimicrobial Resistance Collaborators (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399: 629-655. doi: 10.1016/S0140-6736(21)02724-0.
10. Logan LK (2012) Carbapenem-resistant *Enterobacteriaceae*: an emerging problem in children. Clin Infect Dis 55: 852–859. doi: 10.1093/cid/cis543.
11. Aizawa Y, Shoji T, Ito K, Kasai M, Sakurai H, Toyofuku E, Minami K, Hoshino T, Horikoshi Y (2019) Multidrug-resistant Gram-negative bacterial bloodstream ınfections in children's hospitals in Japan, 2010-2017. Pediatr Infect Dis J 38: 653-659. doi: 10.1097/INF.0000000000002273.
12. Ivády B, Kenesei É, Tóth-Heyn P, Kertész G, Tárkányi K, Kassa C, Ujhelyi E, Mikos B, Sápi E, Varga-Heier K, Guóth G, Szabó D (2016) Factors influencing antimicrobial resistance and outcome of Gram-negative bloodstream infections in children. Infection 44: 309-21. doi: 10.1007/s15010-015-0857-8.
13. De Angelis G, D'Inzeo T, Fiori B, Spanu T, Sganga G (2014) Burden of antibiotic resistant Gram-negative bacterial infections: evidence and limits. J Med Microbiol Diagn 3: 132.
14. Rossolini GM, Mantengoli E, Docquier JD, Musmanno RA, Coratza G (2007) Epidemiology of infections caused by multiresistant Gram-negatives: ESBLs, MBLs, panresistant strains. New Microbiologica 30: 332–339.
15. Oduro-Mensah D, Obeng-Nkrumah N., Bonney EY, Mensah DO, Danso KT, Osei YD, Sackey ST (2016) Genetic characterization of TEM-type ESBL-associated antibacterial resistance in *Enterobacteriaceae* in a tertiary hospital in Ghana. Ann Clin Microbiol Antimicrob 15: 29. doi: 10.1186/s12941-016-0144-2.
16. Marchaim D, Zaidenstein R, Lazarovitch T, Karpuch Y, Ziv T, Weinberger M (2008) Epidemiology of bacteremia episodes in a single center: increase in Gram-negative isolates, antibiotics resistance, and patient age. Eur J Clin Microbiol Infect Dis 27: 1045–1051. doi: 10.1007/s10096-008-0545-z.
17. Maltezou HC (2009) Metallo-beta-lactamases in Gram-negative bacteria: introducing the era of pan-resistance?. Int J Antimicrob Agents 33: 405.e1–405.e4057. doi: 10.1016/j.ijantimicag.2008.09.003.
18. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL (2012) Carbapenemases in *Klebsiella*

pneumoniae and other *Enterobacteriaceae*: an evolving crisis of global dimensions. Clin Microbiol Rev 25: 682–707. doi: 10.1128/CMR.05035-11.
19. Diekema DJ, Pfaller MA, Jones RN, Doern GV, Winokur PL, Gales AC, Sader HS, Kugler K, Beach M (1999) Survey of bloodstream infections due to Gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin Infect Dis 29: 595–607. doi: 10.1086/598640.
20. Kim YK, Pai H, Lee HJ, Park SE, Choi EH, Kim J, Kim JH, Kim EC (2002) Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. Antimicrob Agents Chemother 46: 1481-91. doi: 10.1128/AAC.46.5.1481-1491.2002.
21. Marschall J, Fraser VJ, Doherty J, Warren DK (2009) Between community and hospital: healthcare-associated Gram-negative bacteremia among hospitalized patients. Infect Control Hosp Epidemiol 30: 1050-6. doi: 10.1086/606165.
22. Levy I, Leibovici L, Drucker M, Samra Z, Konisberger H, Ashkenazi S (1996) A prospective study of Gram-negative bacteremia in children. Pediatr Infect Dis J 15: 117-22. doi: 10.1097/00006454-199602000-00006.
23. Al-Hasan MN, Huskins WC, Lahr BD, Eckel-Passow JE, Baddour LM (2011) Epidemiology and outcome of Gram-negative bloodstream infection in children: a population-based study. Epidemiol Infect 139: 791-6. doi: 10.1017/S0950268810001640.
24. Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, Lau YJ, Wang LH, Liu KS, Tsai TY, Lin SY, Hsu MS, Hsu LY, Chang SC (2010) A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant Acinetobacter baumannii. Int J Infect Dis 14: e764-9. doi: 10.1016/j.ijid.2010.02.2254.
25. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis (2005) International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med J 6: 2-8. doi: 10.1097/01.PCC.0000149131.72248.E6.
26. Boev C, Kiss E (2017) Hospital-acquired infections: current trends and prevention. Crit Care Nurs Clin North Am 29: 51–65. doi: 10.1016/j.cnc.2016.09.012.
27. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18: 268–281. doi: 10.1111/j.1469-0691.2011.03570.x.
28. Tsai MH, Chu SM, Hsu JF, Lien R, Huang HR, Chiang MC, Fu RH, Lee CW, Huang YC (2014). Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. Pediatrics 133: e322–e329. doi: 10.1542/peds.2013-1248.
29. Wilson J, Elgohari S, Livermore DM, Cookson B, Johnson A, Lamagni T, Chronias A, Sheridan E (2011) Trends among pathogens reported as causing bacteraemia in England, 2004-2008. Clin Microbiol Infect 17: 451–458. doi: 10.1111/j.1469-0691.2010.03262.x.
30. Pérerz Lopéz A, Ladhani SN, Breathnach A, Planche T, Heath PT, Sharland M (2013) Trends in paediatric nosocomial bacteraemia in a London tertiary hospital. Acta paediatrica 102: 1005–1009. doi: 10.1111/apa.12347.
31. Sarvikivi E, Lyytikäinen O, Vaara M, Saxén H (2008) Nosocomial bloodstream infections in children: an 8-year experience at a tertiary-care hospital in Finland. Clin Microbiol Infect 14: 1072–1075. doi: 10.1111/j.1469-0691.2008.02079.x.
32. Frank M, Gur E, Givon-Lavi N, Peled N, Dagan R, Leibovitz E (2005) Nosocomial bloodstream infections in children and adolescents in southern Israel: a 10-year prospective study (1992-2001). Scand J Infect Dis 37: 177–183. doi: 10.1080/00365540410020956.
33. Haeusler GM, Mechinaud F, Daley AJ, Starr M, Shann F, Connell TG, Bryant PA, Donath S, Curtis N (2013) Antibiotic-resistant Gram-negative bacteremia in pediatric oncology patients--risk factors and outcomes. Pediatr Infect Dis J 32: 723–726. doi: 10.1097/INF.0b013e31828aebc8.
34. Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, Paiva JA, Cakar N, Ma X, Eggimann P, Antonelli M, Bonten MJ, Csomos A, Krueger WA, Mikstacki A, Lipman J, Depuydt P, Vesin A, Garrouste-Orgeas M, Zahar JR, Blot S, Carlet J, Brun-Buisson C, Martin C, Rello J, Dimopoulos G, Timsit JF (2012) Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med 38: 1930–1945. doi: 10.1007/s00134-012-2695-9.
35. Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, Nosari A, Caira M, Spadea A, Busca A, Vianelli N, Tumbarello M, HeMABIS Registry—SEIFEM Group, Italy (2015) Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. Clin Microbiol Infect 21: 337–343. doi: 10.1016/j.cmi.2014.11.022.
36. Aizawa Y, Shoji T, Ito K, Kasai M, Sakurai H, Toyofuku E, Minami K, Hoshino T, Horikoshi Y (2019) Multidrug-resistant Gram-negative bacterial bloodstream infections in children's hospitals in Japan, 2010-2017. Pediatr Infect Dis J 38: 653–659. doi: 10.1097/INF.0000000000002273.
37. Díaz A, Ortiz DC, Trujillo M, Garcés C, Jaimes F, Restrepo AV (2016) Clinical characteristics of carbapenem-resistant *Klebsiella pneumoniae* infections in ill and colonized children in Colombia. Pediatr Infect Dis J 35: 237–241. doi: 10.1097/INF.0000000000000987.
38. Safdar N, Maki DG (2004) The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med 30: 62–67. doi: 10.1007/s00134-003-2045-z.
39. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Microbiol Infect 49: 1–45. doi: 10.1086/599376.
40. Hanna H, Afif C, Alakech B, Boktour M, Tarrand J, Hachem R, Raad I (2004) Central venous catheter-related bacteremia due to Gram-negative bacilli: significance of catheter removal in preventing relapse. Infect Control Hosp Epidemiol 25: 646–649. doi: 10.1086/502455.
41. Quillici MCB, Resende DS, Gonçalves IR, Royer S, Sabino SS, Almeida VF, Ribas RM, Gontijo Filho PP (2021) Gram-negative bacilli bacteremia: a 7 year retrospective study in a

referral Brazilian tertiary-care teaching hospital J Med Microbiol 70. doi: 10.1099/jmm.0.001277.
42. Leblebicioglu H, Esen S, Turkish Nosocomial Urinary Tract Infection Study Group (2003) Hospital-acquired urinary tract infections in Turkey: a nationwide multicenter point prevalence study. J Hosp Infect 53: 207–210. doi: 10.1053/jhin.2002.1362.

Annex – Supplementary items

Supplementary Table 1. Causative organisms in gram-negative culture growth.

Organism	N (%)
Klebsiella pneumoniae	23 (18.7)
Escherichia coli	19 (15.4)
Stenotrophomonas maltophilia	15 (12.2)
Pseudomonas aeruginosa	14 (11.4)
Serratia marcescens	10 (8.1)
Acinetobacter lwoffii	7 (5.7)
Enterobacter cloacae complex	7 (5.7)
Acinetobacter baumannii	6 (4.9)
Klebsiella oxytoca	5 (4.1)
Enterobacter aerogenes	3 (2.4)
Acinetobacter pittii	2 (1.6)
Acinetobacter ursingii	2 (1.6)
Pseudomonas oryzihabitans	2 (1.6)
Acinetobacter haemolyticus	1 (0.8)
Pseudomonas stutzeri	2 (1.6)
Acinetobacter radioresistens	1 (0.8)
Enterobacter hormaechei	1 (0.8)
Serratia liquefaciens	1 (0.8)
Pseudomonas putida	1 (0.8)
Proteus mirabilis	1 (0.8)

Supplementary Table 2. Treatment regimens and mean treatment duration of non-survivors are shown; number of patients (mean or median treatment duration).

	CTX	CFD	CFP	PIP-T	MEM	MEM + GEN	MEM + AMI	MEM + COL	ETP + MEM + COL	CIP + TRI-S
E. coli	-	-	-	-	5 (10)	-	-	-	-	-
K. pneumoniae	-	-	-	-	3 (13)	-	-	-	-	-
P. aeruginosa	-	-	-	-	2 (IQR:1-4)	-	-	-	-	-
S. marcescens	-	-	-	-	2 (10)	-	-	-	-	-
S. maltophilia	-	-	-	-	-	-	-	-	-	1(3)

AMI: Amikacin; CFD: Ceftazidime; CIP: Ciprofloxacin ; COL: Colistin; CTX: Cefriaxone ; CFP: Cefepime ; GEN: Gentamicin; MEM: Meropenem; ETP: Ertapenem; TRI-S: Trimethoprim–sulfamethoxazole; PIP-T: Piperacillin–tazobactam. IQR: Interquartile rate.