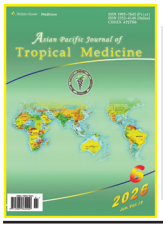

Original Article

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Clinical outcomes and multidrug resistance patterns of rare Gram-negative bloodstream infections: An 8-year analysis from a tertiary pediatric hospital

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ABSTRACT

Objective: To evaluate the clinical characteristics, risk factors, antimicrobial susceptibility profiles, and outcomes of bloodstream infections caused by rare Gram-negative bacteria in a tertiary pediatric center.

Methods: A retrospective analysis was conducted on pediatric patients (0-18 years) with rare Gram-negative bloodstream infections growth in blood cultures between 2016 and 2023. Common pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas* spp., and *Acinetobacter* spp.) were excluded to focus on unusual isolates.

Results: A total of 394 patients were included in the study. Their median age was 21.5 months and 237 (60.2%) were male. The cohort had a high prevalence of chronic underlying diseases (94.0%) and a median hospital stay of 27 (16, 49) days. Central venous catheters (35.8%) and recent blood product transfusions (35.8%) were the most frequent predisposing factors. The most prevalent isolates were *Serratia* spp. (20.1%), *Stenotrophomonas maltophilia* (17.5%), and *Enterobacter* spp. (15.2%). High rates of intrinsic and acquired resistance were observed: 100% of *Serratia* isolates were resistant to trimethoprim/sulfamethoxazole, and *Elizabethkingia meningoseptica* demonstrated extensive carbapenem resistance. Resistance to co-trimoxazole in *Stenotrophomonas maltophilia* was 0%. All-cause mortality was 13.7%, whereas infection-related mortality was 1.1%, specifically associated with *Aeromonas* spp. (10.0%), *Comamonas testosteroni* (25.0%), and *Enterobacter* spp (3.3%).

Conclusions: Rare Gram-negative bacteria bloodstream infections in children represent a significant diagnostic and therapeutic challenge due to unpredictable resistance patterns. Our data suggest that empirical therapy for high-risk pediatric patients should be periodically reviewed to include coverage for these emerging pathogens, especially in those with indwelling devices and chronic comorbidities.

KEYWORDS: Rare Gram-negative bacteremia; Children; Resistance; Pediatric bloodstream infections

Summary

Question: What are the clinical features, antimicrobial resistance, and mortality risk factors of rare Gram-negative bloodstream infections in hospitalized children?

Findings: Among 394 pediatric cases, common pathogens were *Serratia* spp., *Stenotrophomonas maltophilia* and *Enterobacter* spp. with complex resistance. Imipenem resistance peaked at 28.6% in 2023. Overall mortality was 13.7%, and direct mortality (1.1%) was mainly caused by *Comamonas testosteroni*, *Aeromonas* spp. and *Enterobacter* spp.

Meaning: Rare Gram-negative bacteremia leads to high mortality in children, highlighting the need for continuous surveillance and optimized carbapenem therapy.

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1. Introduction

Gram-negative bloodstream infections are a significant cause of mortality and morbidity in children[1]. They are commonly observed in preterm infants and immunocompromised children[2]. Numerous risk factors exist, including prolonged steroid use, intensive care unit admission, chemotherapy, and central venous catheterization[3]. Increasing antimicrobial resistance, particularly with the proliferation of multidrug-resistant Gram-negative microorganisms, complicates the management of these patients, leading to increased morbidity, mortality, and prolonged hospital stays[4]. Over the years, Gram-negative bloodstream infections have shown an increase; species such as *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella pneumoniae*, and *Escherichia coli* are among the most frequently isolated pathogens[4–6].

Determining the epidemiological and microbiological profiles of bacteremia caused by rare Gram-negative bacteria is critically important for optimizing empirical treatment strategies[7]. Understanding the spectrum and resistance dynamics of such pathogens will contribute to the development of infection control measures and the identification of targeted antimicrobial therapies[8]. This study aimed to identify the clinical characteristics, risk factors, antibiotic susceptibility, and mortality outcomes of bloodstream infections caused by rare Gram-negative microorganisms, excluding *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella pneumoniae*, and *Escherichia coli*. With this retrospective study, we aimed to provide guidance for clinical practices by evaluating the challenges and potential risk factors in the diagnosis and treatment processes of these rare pathogens.

2. Methods

2.1. Study group

In this retrospective study conducted at a tertiary hospital, data on patients aged 0-18 years with Gram-negative bacteria isolated from blood cultures between January 13, 2016, and September 21, 2023, was retrieved from microbiology laboratory records. Blood culture growths attributed to *Acromabacter* spp., *Aeromonas* spp., *Bordetella* spp., *Brevundimonas diminuta*, *Burkholderia* spp., *Chryseobacterium* spp., *Citrobacter freundii*, *Comamonas testosteroni*, *Elizabethkingia meningoseptica*, *Enterobacter* spp., *Ewingella americana*, *Haemophilus influenzae*, *Moraxella* (*branhamella*) *catarrhalis*, *Morganella morganii*, *Neisseria* spp., *Pantoea* spp., *Proteus mirabilis*, *Salmonella* spp., *Serratia* spp., *Shewanella* spp., *Sphingomonas* spp., and *Stenotrophomonas maltophilia* were included in the study. Patient demographic characteristics, underlying diseases, predisposing factors, isolated bacteria and antibiotic susceptibility test results, laboratory parameters, and prognoses were analyzed. Exclusion criteria were as follows: a) patients whose file information was inaccessible, b) patients without clinical signs of bacteremia, c) patients transferred to another hospital before completing treatment, d) bacteremias caused by *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella pneumoniae*, and *Escherichia coli* e) microorganisms that could not be definitively identified as the causative agent (*Hafnia alvei*, *Aerococcus viridans*, *Actinomyces odontolyticus*, *Ochrobactrum anthropi*, *Oligella ureolytica*, *Providencia rettgeri*, *Sphingobacterium thalpophium*, *Alcaligenes faecalis*, *Dermacoccus nishinomiyaensis*, *Delftia acidovorans*).

A total of 2 901 Gram-negative microorganism growths were detected in catheter and peripheral blood cultures. Of these, 938 were *Klebsiella pneumoniae*, 619 were *Acinetobacter* spp., 340 were *Pseudomonas* spp., and 319 were *Escherichia coli*. Seventy-seven patients were excluded from the study because they were over 18 years old, despite their admission to pediatric wards. A total of 608 culture growths were observed due to rare Gram-negative microorganisms. According to the exclusion criteria, 214 patients were excluded from the study. Patients who still had positive blood cultures three days after the initiation of antimicrobial treatment were considered to have persistent bacteremia[9], and growths related to persistent bacteremia were counted as one bacteremia episode, leading to the inclusion of 394 patients in the study. The diagram of the study is shown in Figure 1.

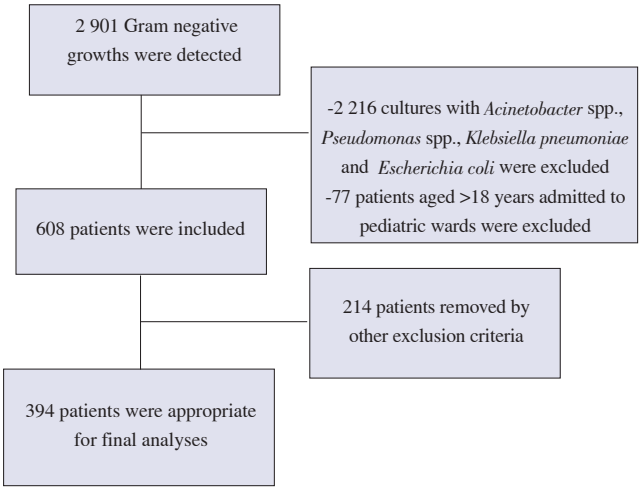

Figure 1. The diagram of the study.

2.2. Microbiological identification

Blood samples were cultured and identified at the Medical Microbiology Unit of Çukurova University. Blood cultures were incubated for five days in a fully automated blood culture system, BACTEC-FX (Becton Dickinson, Sparks, MD, USA). Samples signaling growth were examined under Biosafety Level-2 conditions using Gram staining and methylene blue staining. Subsequently, they were subcultured onto 5% sheep blood agar, MacConkey agar, and chocolate agar (RTA Laboratories, Türkiye) using the single colony streaking method and incubated at 37 ℃ for 24-48 hours. Identification of the grown isolates and antimicrobial susceptibility testing were performed using conventional methods and the VITEK 2 Compact ID/AST automated system (bioMérieux, Marcyl'Étoile, France). The antibiotic resistance profiles of the isolates were evaluated according to the guidelines of the European Society of Clinical Microbiology and Infectious Diseases. This evaluation provides information on treatment options by revealing the resistance patterns of each rare Gram-negative bacterium against specific antimicrobial agents. In particular, the identification of multidrug-resistant strains is a fundamental step for revising empirical treatment protocols and developing strategies to prevent resistance development. Accordingly, the antimicrobial susceptibilities of the bacterial isolates included in the study were determined using the VITEK 2 automated system, and the obtained data were interpreted according to the European Committee on Antimicrobial Susceptibility Testing clinical breakpoints[10].

2.3. Statistical analysis

Statistical analyses of the data obtained in the study were performed using IBM SPSS Statistics Version 23.0 software. Demographic and clinical characteristics of the included patients were summarized, with categorical variables expressed as number (n) and percentage (%); continuous variables were expressed as mean, standard deviation, or median (Q1, Q3). *Chi*-square test of independence was used to evaluate relationships between categorical variables. One-way analysis of variance was applied for inter-group comparisons of numerical variables. In all statistical analyses, a P-value < 0.05 was considered statistically significant.

2.4. Ethical approval

The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Approval Date: 14/06/2024, Approval No: 2024/06-145). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

3. Results

3.1. Baseline clinical characteristics of included patients

A total of 394 patients were included in the study. Their median age was 21.5 months and 237 (60.2%) were male. The demographic characteristics, underlying diseases, source of bacteremia, risk factors, and mortality rates of the patients are shown in Table 1.

Among the Gram-negative bacteria encompassing *Acromabacter* spp., *Aeromonas* spp., *Bordetella* spp., *Brevundimonas diminuta*, *Burkholderia* spp., *Chryseobacterium* spp., *Citrobacter freundii*, *Comamonas testosteroni*, *Elizabethkingia meningoseptica*, *Enterobacter* spp., *Ewingella americana*, *Haemophilus influenzae*, *Moraxella* (*branhamella*) *catarrhalis*, *Morganella morganii*, *Neisseria* spp., *Pantoea* spp., *Proteus mirabilis*, *Salmonella* spp., *Serratia* spp., *Shewanella* spp., *Sphingomonas* spp., and *Stenotrophomonas maltophilia*, the most frequently observed were *Serratia* spp. (n=79, 20.1%), *Stenotrophomonas maltophilia* (n=69, 17.5%), and *Enterobacter* spp. (n=60, 15.2%).

Of the detected infections, 97.2% were characterized as healthcare-associated infections. Culture growth was observed at a median of 10 (4, 22) days after hospitalization. The median treatment duration was 12 (7, 17) days, and the median length of hospital stay was 27 (6, 49) days. Blood cultures became negative at a median of 4 (3, 6) days after initiation of treatment. Underlying diseases were present in 94.0% of the patients. The origin of bacteremia was respiratory infections (30.8%), primary bacteremia (29.6%), catheter-related infection (16.5%), gastrointestinal system (11.9%), genitourinary system (6.1%), musculoskeletal system and skin (3.3%), cardiac system (1.1%) and central nervous system (0.8%) Predisposing risk factors were screened, and four (1.1%) patients had no underlying risk factors.

Table 1. Demographic data, underlying diseases, origin of bacteriemia, risk factors, mortality rate of patients according to Gram-negative bacteria causing bloodstream infection (*n*=394).

Characteristics	*n* (%)
Age, median (Q1, Q3), months	21.5 (0.0, 216.0)
Sex	
Male	237 (60.2)
Female	157 (39.8)
Underlying diseases	
Cardiac diseases	79 (20.1)
Hematologic malignacy	51 (12.9)
Oncologic malignancy	26 (6.6)
Premature birth	46 (11.7)
Neurologic diseases	35 (8.9)
Metabolic diseases	31 (7.9)
Renal diseases	21 (5.3)
Primary immundeficiencies	21 (5.3)
Gastroenterologic diseases	15 (3.8)
Hematologic nonmalign disease	8 (2.0)
Endocrinologic diseases	2 (0.5)
Other diseases	39 (9.9)
Risk factors	
Catheter	141 (35.8)
Blood product use	141 (35.8)
Nasogastric probe	115 (29.2)
Steroid use	91 (23.1)
Chemotherapy	77 (19.5)
Total parenteral nutrition	61 (15.5)
Urinary catheter	43 (10.9)
Tracheostomy	36 (9.1)
Hemodialysis+peritoneal dialysis	16 (4.1)
Gastrostomy	14 (3.6)
External ventricular drainage/ ventriculo-peritoneal shunt	4 (1.1)

Data were expressed as *n* (%) unless otherwise indicated.

3.2. Correlation analysis of pathogen type with bacteremia source and hospitalization department

To evaluate the relationship between microorganism type and the source of bacteremia, the *Chi*-square test of independence was applied. A statistically significant relationship was found between these two parameters. *Stenotrophomonas maltophilia* was more frequently detected in catheter-related and respiratory system-related bloodstream infections; *Sphingomonas* spp. in primary bacteremia; and *Enterobacter* spp. in primary bacteremia, catheter-related, and gastrointestinal system-related bloodstream infections. The *Chi*-square test of independence was also performed to evaluate the relationship between the microorganism type and the patient's hospitalization service. A significant relationship was found between these two parameters (χ^2=579.06, df=132, P<0.001). Microorganisms with a significant relationship to the hospitalization service are shown in Table 2.

3.3. Antibiotic resistance profiles of isolated pathogens

Susceptibility tests were performed for ampicillin, amoxicillin+clavulanic acid, piperacillin+tazobactam, ceftriaxone, cefotaxime, ceftazidime, cefepime, meropenem, imipenem, amikacin, gentamicin, ciprofloxacin, trimethoprim/sulfamethoxazole, tigecycline, colistin, and levofloxacin. The comprehensive antibiotic resistance profiles of the isolated microorganisms are detailed in Table 3. When examining the antibiotic resistance rates of microorganisms, the antibiotics to which they showed the highest resistance were: *Acromabacter* spp. to ciprofloxacin (76.9%), amikacin (61.5%), cefepime (46.2%), gentamicin (46.2%); *Aeromonas* spp. to ceftazidime (30%), imipenem (30%); *Bordetella* spp. to

Table 2. Hospitalization services of patients and microorganisms significantly associated with hospitalization service.

Hospitalization service	*N* (%)	Microorganisms significantly associated with the hospitalization service*
Pediatric services	96 (24.4)	*Acromacter* spp. *Enterobacter* spp *Serratia* spp. *Sphingomonas* spp. *Stenotrophomonas maltophilia*
Pediatric hematology oncology and bone marrow transplantation services	87 (22.1)	*Burkholderia* spp. *Enterobacter* spp *Sphingomonas* spp. *Stenotrophomonas maltophilia*
Pediatric intensive care unit	71 (18.0)	*Acromabacter* spp. *Sphingomonas* spp.
Neonatal intensive care unit	64 (16.2)	*Burkholderia* spp. *Serratia* spp.
Surgical intensive care unit	47 (11.9)	*Serratia* spp.

*P<0.001, χ^2: 579.06, df: 132.

Table 3. Antibiotic resistance distribution by microorganisms.

Bacteria	*N* (%)[#]	AMP S/I/R (%)[*]	AMC S/I/R (%)[*]	TZP S/I/R (%)[*]	CTR S/I/R (%)[*]	CTX S/I/R (%)[*]	CAZ S/I/R (%)[*]	CEF S/I/R (%)[*]	MER S/I/R (%)[*]	IMI S/I/R (%)[*]	AMI S/I/R (%)[*]	GEN S/I/R (%)[*]	CIP S/I/R (%)[*]	LEV S/I/R (%)[*]	SXT S/I/R (%)[*]	COL S/I/R (%)[*]
Serratia spp.	79 (20.1)	-	-	56/2/20 (25.3)	-	-	56/-/20 (25.3)	68/1/17 (21.5)	55/2/16 (20.3)	48/1/16 (20.3)	60/6/11 (13.9)	70/-/7 (8.9)	-/75/4 (5.1)	49/16/3 (3.8)	-/-/79IR	2/-/73IR
Stenotrophomonas maltophilia	69 (17.5)	-	-	-	-	-	2/-/- (0.0)	-	-	-	-	-	-	15/-/- (0.0)	56/13/- (0.0)	-
Enterobacter spp.	60 (15.2)	-	-	45/1/12 (20.0)	16/-/3 (5)	-	41/2/12 (20.0)	44/3/6 (10.0)	50/1/4 (6.7)	22/1/6 (10.0)	50/3/4 (6.7)	49/-/8 (13.3)	45/1/10 (16.7)	18/6/2 (3.3)	45/-/12 (20.0)	48/-/3 (5.0)
Neisseria spp.	22 (5.6)	-/1//4 (18.2)	-/-/2 (9.1)	-	-	-/-/1 (4.5)	-	-	-	-/-/1 (4.5)	-/-/4 (18.2)	-	-/-/3 (13.6)	-	-/-/1IR	-
Sphingomonas spp.	20 (5.1)	4/-/3 (15.0)	5/-/2 (10.0)	10/1/6 (30.0)	3/-/2 (10.0)	4/-/2 (10.0)	5/1/9 (45.0)	5/1/9 (45.0)	16/1/1 (5.0)	18/-/- (0.0)	10/2/- (0.0)	16/-/3 (15.0)	16/1/3 (15.0)	-	9/1/1 (5.0)	-/-/11IR
Burkholderia spp.	16 (4.1)	-	-	5/2/9 (56.3)	-	-	11/-/5 (31.3)	5/-/11 (68.8)	11/3/2 (12.5)	7/-/8IR	9/2/5IR	8/-/7 (43.8)	4/3/9 (56.3)	8/-/7 (43.8)	1/-/-	1/-/12IR
Pantoea spp.	14 (3.6)	-	-	9/1/1 (7.1)	-	-	5/1/3 (21.8)	8/-/1 (7.1)	11/-/1 (7.1)	10/-/1 (7.1)	13/-/1 (7.1)	14/-/- (0.0)	-/-/14 (100)	11/-/- (0.0)	-/-/14 (100.0)	8/-/2 (14.2)
Salmonella group	14 (3.6)	-	-	12/-/1 (0.0)	-	-	10/-/4 (28.6)	8/-/3 (21.4)	13/-/1 (7.1)	4/-/- (0.0)	14/-/- (0.0)	14/-/- (0.0)	-/10/2 (14.3)	4/-/2 (14.3)	-/-/14 (100.0)	12/-/- (0.0)
Shewanella spp.	13 (3.3)	-	-	10/-/2 (15.4)	-	-	-/-/12 (92.3)	1/5/7 (53.8)	10/1/2 (15.4)	10/-/3 (23.1)	11/1/1 (7.7)	11/-/- (0.0)	-/1/12 (92.3)	1/8/3 (23.1)	-/-/2 (15.4)	11/-/- (0.0)
Acromabacter spp.	13 (3.3)	-	-	13/-/- (0.0)	-	-	10/-/- (0.0)	1/4/6 (46.2)	12/1/- (0.0)	12/-/1 (7.7)	2/3/8 (61.5)	1/3/6 (46.2)	-/3/10 (76.9)	-/1/- (0.0)	9/-/- (0.0)	3/-/1 (7.7)
Aeromonas spp.	10 (2.5)	-	-	10/-/- (0.0)	-	-	6/-/3 (30.0)	9/-/1 (10.0)	10/-/- (0.0)	6/-/3 (30.0)	10/-/- (0.0)	9/-/- (0.0)	9/1/- (0.0)	8/-/- (0.0)	3/-/- (0.0)	6/-/- (0.0)
Chryseobacterium spp.	10 (2.5)	-	-	1/1/7 (70.0)	-	-	2/-/8 (80.0)	1/6/3 (30.0)	-/-/10IR	1/-/9IR	-/1/9IR	-/1/9IR	8/2/- (0.0)	7/1/2 (20.0)	6/1/1 (10.0)	-/-/3 (30.0)
Moraxella (branhamella) catarrhalis	10 (2.5)	1/-/2 (20.0)	3/-/1 (10.0)	7/-/1 (10.0)	-/-/1 (10.0)	-/-/1 (10.0)	3/-/4 (40.0)	5/-/2 (20.0)	10/-/- (0.0)	8/-/- (0.0)	5/-/- (0.0)	5/-/1 (10.0)	6/-/2 (20.0)	4/-/- (0.0)	3/-/2IR	2/-/- (0.0)
Brevundimonas diminuta	9 (2.3)	-	-	2/1/2 (22.2)	-	-	3/-/3 (33.3)	4/1/2 (22.2)	6/-/3 (33.3)	4/1/4 (44.4)	3/1/5 (55.5)	4/1/3 (33.3)	4/-/5 (55.5)	6/-/2 (22.2)	3/-/2 (22.2)	2/-/3IR
Proteus mirabilis	7 (1.8)	-	-	6/-/- (0.0)	-	-	3/2/1 (14.3)	4/-/2 (28.6)	3/-/- (0.0)	-/1/1 (14.3)	5/-/1 (14.3)	2/-/4 (57.1)	-/2/4 (57.1)	1/-/1 (14.3)	1/-/5 (71.4)	-/-/4IR
Citrobacter freundii	6 (1.5)	IR	-/-/1 (16.6)	4/-/2 (33.3)	-	-	4/-/2 (33.3)	4/-/2 (33.3)	5/-/1	2/-/-	6/-/-	6/-/-	5/-/1	2/-/- (0.0)	4/-/2 (33.3)	3/-/- (0.0)
Elizabethkingia meningoseptica	6 (1.5)	-	-	1/-/5 (83.3)	-	-	1/-/4 (66.7)	1/-/5 (83.3)	1/-/5IR	-/-/5IR	1/-/5IR	1/-/4IR	4/2/- (0.0)	5/-/- (0.0)	5/-/- (0.0)	-/-/1 (16.6)
Bordetella spp.	5 (1.3)	-	-	3/-/- (0.0)	-	-	3/-/- (0.0)	1/-/3 (60.0)	2/2/- (0.0)	3/1/- (0.0)	1/1/3 (60.0)	1/-/4 (80.0)	-/-/4 (80.0)	1/-/4 (80.0)	1/-/- (0.0)	3/-/1 (20)
Comamonas testosteroni	4 (1)	-	-	2/-/1 (25.0)	-	-	2/-/- (0.0)	3/-/- (0.0)	4/-/- (0.0)	4/-/- (0.0)	2/1/1 (25.0)	1/-/2 (50.0)	2/-/2 (50.0)	1/-/2 (50.0)	-/-/2 (50.0)	3/-/- (0.0)
Morganella morganii	3 (0.8)	IR	-	3/-/- (0.0)	-	-	3/-/- (0.0)	3/-/- (0.0)	3/-/- (0.0)	2/-/1 (33.3)	3/-/- (0.0)	2/-/1 (33.3)	3/-/- (0.0)	2/-/- (0.0)	2/-/1 (33.3)	-/-/3IR
Haemophilus influenzae	2 (0.5)	1/-/- (0.0)	1/-/1 (50.0)	-	-	-	-	-	1/-/- (0.0)	2/-/- (0.0)	-		2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	-
Ewingella americana	2 (0.5)	-	-	2/-/- (0.0)	-	-	1/-/- (0.0)	-	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)	2/-/- (0.0)

[#]Number of microorganism (microorganism rate). [*]Resistance rate. AMP: Ampicillin; AMC: Amoxicillin+clavulanic acid; TZP: Piperacillin+tazobactam; CTR: Ceftriaxone; CTX: Cefotaxime; CAZ: Ceftazidime; CEF: Cefepime; MER: Meropenem; IMI: Imipenem; AMI: Amikacin; GEN: Gentamicin; CIP: Ciprofloxacin; SXT: Trimethoprim/ sulfamethoxazole; TGC: Tigecycline; COL: Colistin; LEV: Levofloxacin; IR: Intrinsic resistance; S: Susceptible; I: Intermediate; R: Resistant. -: not available.

Table 4. Changes in meropenem resistance rates of selected microorganisms by year.

Bacteria	*N* (%)[#]	2016		2017		2018		2019		2020		2021		2022		2023	
		TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)	TN	*n/N* (%)
Serratia spp.	79 (20.1)	15	2/15 (13.3)	8	2/8 (25.0)	18	4/18 (22.2)	10	2/10 (20.0)	8	0/8 (0.0)	8	2/8 (25.0)	10	4/10 (40.0)	2	1/2 (50.0)
Enterobacter spp.	60 (15.2)	12	0/12 (0.0)	11	2/11 (18.2)	5	0/5 (0.0)	7	0/7 (0.0)	7	0/7 (0.0)	6	1/6 (16.6)	8	1/8 (12.5)	4	0/4 (0.0)
Neisseria spp.	22 (5.6)	3	0/3 (0.0)	8	0/8 (0.0)	8	0/8 (0.0)	3	0/3 (0.0)	0	-	0	-	0	-	0	-
Sphingomonas spp.	20 (5.1)	5	0/5 (0.0)	3	1/3 (33.3)	3	0/3 (0.0)	1	0/1 (0.0)	2	0/2 (0.0)	2	0/2 (0.0)	1	0/1 (0.0)	3	0/3 (0.0)
Burkholderia spp.	16 (4.1)	1	0/1 (0.0)	3	0/3 (0.0)	0	-	4	0/4 (0.0)	3	1/3 (33.3)	2	1/2 (50.0)	2	0/2 (0.0)	1	0/1 (0.0)
Pantoea spp.	14 (3.6)	4	1/4 (25.0)	1	0/1 (0.0)	1	0/1 (0.0)	3	0/3 (0.0)	2	0/2 (0.0)	2	0/2 (0.0)	1	0/1 (0.0)	0	-
Salmonella group	14 (3.6)	1	0/1 (0.0)	2	0/2 (0.0)	2	0/2 (0.0)	2	0/2 (0.0)	3	0/3 (0.0)	3	0/3 (0.0)	1	0/1 (0.0)	0	-
Shewanella spp.	13 (3.3)	0	-	11	0/11 (0.0)	0	-	0	-	1	1/1 (100.0)	0	-	0	-	1	171 (100.0)
Acromabacter spp.	13 (3.3)	3	0/3 (0.0)	1	0/1 (0.0)	0		1	0/1 (0.0)	1	0/1 (0.0)	3	0/3 (0.0)	2	0/2 (0.0)	2	0/2 (0.0)
Aeromonas spp.	10 (2.5)	0		3	0/3 (0.0)	1	0/1 (0.0)	2	0/2 (0.0)	0		0		4	0/4 (0.0)	0	
Moraxella (branhamella) catarrhalis	10 (2.5)	2	0/2 (0.0)	1	0/1 (0.0)	4	0/4 (0.0)	1	0/1 (0.0)	1	0/1 (0.0)	0	-	1	0/1 (0.0)	0	-
Brevundimonas diminuta	9 (2.3)	0	-	1	0/1 (0.0)	3	2/3 (66.6)	0	-	1	0/1 (0.0)	1	1/1 (100.0)	1	0/1 (0.0)	2	0/2 (0.0)
Proteus mirabilis	7 (1.8)	0		0	-	1	0/1 (0.0)	1	0/1 (0.0)	0	-	3	0/3 (0.0)	2	0/2 (0.0)	0	-
Citrobacter freundii	6 (1.5)	1	0/1 (0.0)	0	-	1	0/1 (0.0)	1	1/1 (100.0)	1	0/1 (0.0)	2	0/2 (0.0)	0	-	0	-
Bordetella spp.	5 (1.3)	1	0/1 (0.0)	2	0/2 (0.0)	1	0/1 (0.0)	1	0/1 (0.0)	0	-	0	-	0	-	0	-
Comamonas testosteroni	4 (1.0)	1	0/1 (0.0)	2	0/2 (0.0)	0	-	0	-	0	-	0	-	0	-	1	0/1 (0.0)
Morganella morganii	3 (0.8)	1	0/1 (0.0)	1	0/1 (0.0)	0	-	0	-	1	0/1 (0.0)	0	-	0	-	0	-
Haemophilus influenzae	2 (0.5)	0	-	2	0/2 (0.0)	0	-	0	-	0	-	0	-	0	-	0	-
Ewingella americana	2 (0.5)	1	0/1 (0.0)	0	-	0	-	0	-	0	-	1	0/1 (0.0)	0	-	0	-

[#]Number of microorganism (microorganism rate). TN: Total number of isolates, *n/N* (%): Number of meropenem-resistant isolates/Total number of isolates in that year (meropenem resistance rate). -: not available.

ciprofloxacin (80.0%), levofloxacin (80.0%), amikacin (60.0%), cefepime (60.0%); *Brevundimonas diminuta* to ciprofloxacin (55.6%), amikacin (55.6%), imipenem (44.4%); *Burkholderia* spp. to cefepime (68.8%), piperacillin+tazobactam (56.3%), ciprofloxacin (56.3%); *Chryseobacterium* spp. to ceftazidime (80%), piperacillin+tazobactam (70.0%); *Citrobacter freundii* to piperacillin+tazobactam (33.3%), ceftazidime (33.3%), cefepime (33.3%), trimethoprim/ sulfamethoxazole (33.3%); *Comamonas testosteroni* to gentamicin (50.0%), ciprofloxacin (50.0%), levofloxacin (50.0%), trimethoprim/ sulfamethoxazole (50.0%); *Elizabethkingia meningoseptica* to piperacillin+tazobactam (83.3%), cefepime (83.3%), ceftazidime (66.7%); *Enterobacter* spp. to piperacillin+tazobactam (20.0%), ceftazidime (20.0%), trimethoprim/ sulfamethoxazole (20.0%); *Haemophilus influenzae* to amoxicillin+clavulanic acid (50.0%); *Moraxella* (*branhamella*) *catarrhalis* to cefepime (40.0%); *Morganella morganii* to imipenem (33.3%), gentamicin (33.3%), trimethoprim/ sulfamethoxazole (33.3%); *Neisseria* spp. to amikacin (18.2%), ampicillin (18.2%); *Pantoea* spp. to ciprofloxacin (100.0%), trimethoprim/ sulfamethoxazole (100.0%), ceftazidime (21.4%); *Proteus mirabilis* to trimethoprim/ sulfamethoxazole (71.4%), gentamicin (57.1%), ciprofloxacin (57.1%); *Salmonella* spp. to trimethoprim/sulfamethoxazole (100.0%), ceftazidime (28.6%), cefepime (21.4%); *Serratia* spp. to piperacillin+tazobactam (25.3%), ceftazidime (25.3%), cefepime (21.5%); *Shewanella* spp. to ceftazidime (92.3%), ciprofloxacin (92.3%), cefepime (53.9%); *Sphingomonas* spp. to cefepime (45.0%), ceftazidime (45.0%), piperacillin+tazobactam (30.0%). No resistance was detected in *Stenotrophomonas maltophilia* and *Ewingella americana*. The distribution of bloodstream infections, and their susceptibility and resistance to antibiotics, are shown in Table 3.

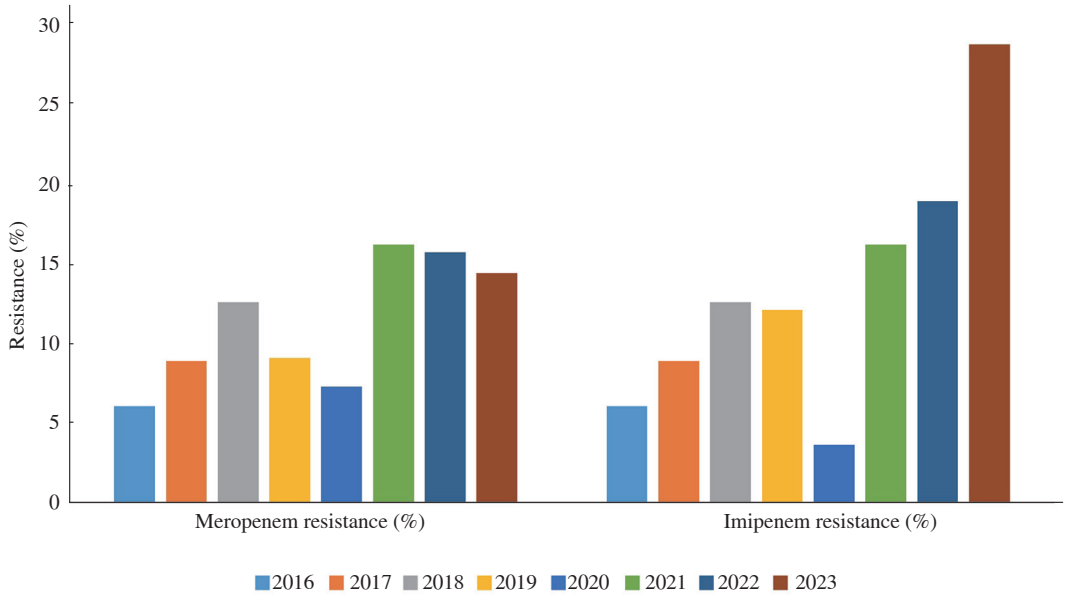

Figure 2. Changes in meropenem and mipenem resistance over the years.

3.4. Annual trends in carbapenem resistance

The annual changes in meropenem resistance rates for certain microorganisms are presented in Table 4. The numerical distribution of these microorganisms and their resistance to meropenem were examined year by year between 2016 and 2023. *Serratia* spp., which constituted the highest proportion of the isolates (20.1%, *n*=79), demonstrated an upward trend in meropenem resistance, climbing from 13.3% in 2016 to a peak of 50.0% by 2023. In contrast, *Enterobacter* spp., the second most prevalent group (15.2%, *n*=60), maintained a relatively low and fluctuating resistance profile, peaking at 18.2% in 2017 and remaining fully susceptible in several years. Notably, despite their lower isolation frequencies, certain opportunistic pathogens exhibited sporadic, high-grade resistance spikes; specifically, *Shewanella* spp. reached 100% resistance in both 2020 and 2023, while *Brevundimonas diminuta* showed 100% resistance in 2021. Conversely, stable and complete susceptibility (0% meropenem resistance) throughout the study period was sustained by several species, including *Neisseria* spp., *Salmonella* group, *Comamonas testosteroni*, *Acromabacter* spp, *Aeromonas* spp, *Moraxella catarrhalis*, *Proteus mirabilis*, *Morganella morganii*, *Haemophilus influenzae*, *Ewingella americana* and *Bordetella* spp. The annual evolution of overall meropenem and imipenem resistance rates from 2016 to 2023 is illustrated in Figure 2. Meropenem and imipenem were exclusively selected for annual resistance trend analysis as they were the only carbapenems routinely tested in our institution's susceptibility panels and represent critical, restricted-use antimicrobials requiring strict monitoring. Both carbapenems exhibited an identical baseline resistance rate of 6.0% in 2016, followed by a gradual increase that peaked at 12.5% in 2018. Notably, a sharp decline in resistance was observed for both agents in 2020, dropping to 7.2% for meropenem and 3.6% for imipenem. Post-2020, resistance rates for both antibiotics experienced a substantial rebound. While meropenem resistance plateaued slightly in the final years, fluctuating between 14.3% and 16.1%, imipenem resistance demonstrated a continuous escalation, reaching a study peak of 28.6% in 2023.

3.5. Inflammatory biomarker levels and pathogen correlation

We examined the laboratory parameters of our patients The median levels of C-reactive protein (CRP) and procalcitonin were 17.3 (3.0, 61.8) mg/L and 1.4 (0.44, 5.64) ng/mL, respectively. In our study, One-way analysis of variance was performed to investigate the potential effect of different Gram-negative microorganism types on CRP levels. It was concluded that there was no statistically significant relationship between microorganism groups and CRP levels (P>0.05).

3.6. Patient mortality analysis

The overall mortality rate for all patients was found to be 13.7%, and the bacteremia-related mortality rate was 1.1%. Bacteremia-related mortality was defined as death occurring within 14 days of the positive blood culture due to active sepsis or septic shock, with no other identifiable non-infectious cause. Causes of mortality other than bacteremia included postoperative complications due to congenital heart disease, terminal stage malignancy, prematurity-

Table 5. Mortality rate of patients according to microorganisms.

Bacteria	*N* (%)	Species-specific mortality , *n*/*N* (%)
Acromabacter spp.	13 (3.3)	4/13 (30.7)
Aeromonas spp.	10 (2.5)	4/10 (40.0)
Bordetella spp.	5 (1.3)	2/5 (40.0)
Brevundimonas diminuta	9 (2.3)	-
Burkholderia spp.	16 (4.1)	-
Chryseobacterium spp.	10 (2.5)	1/10 (10.0)
Citrobacter freundii	6 (1.5)	3/6 (50.0)
Comamonas testosteroni	4 (1.0)	1/4 (25.0)
Elizabethkingia meningoseptica	6 (1.5)	1/6 (16.7)
Enterobacter spp.	60 (15.2)	8/60 (13.3)
Ewingella americana	2 (0.5)	1/2 (50.0)
Haemophilus influenzae	2 (0.5)	-
Moraxella (branhamella) catarrhalis	10 (2.5)	1/10 (10.0)
Morganella morganii	3 (0.8)	-
Neisseria spp.	22 (5.6)	1/22 (4.5)
Pantoea spp.	14 (3.6)	-
Proteus mirabilis	7 (1.8)	-
Salmonella group	14 (3.6)	-
Serratia spp.	79 (20.1)	-
Shewanella spp.	13 (3.3)	-
Sphingomonas spp.	20 (5.1)	2/20 (10.0)
Stenotrophomonas maltophilia	69 (17.5)	25 (36.2)
Total	394 (100.0)	54/394 (13.7)

NA: not available.

related complications, and deaths due to major trauma. In our study, the most mortal agents were *Ewingella americana* (50.0%), *Citrobacter freundii* (50.0%), *Aeromonas* spp. (40.0%), *Bordetella* spp. (40.0%), and *Stenotrophomonas maltophilia* (36.2%). When analyzing pathogen-specific outcomes, the bacteremia-related mortality rates directly attributed to individual microorganisms were 25.0% for *Comamonas testosteroni*, 10.0% for *Aeromonas* spp., and 3.3% for *Enterobacter* spp. Patients classified under bacteremia-related mortality experienced rapid clinical deterioration and death immediately following the isolation of the specific pathogens. Given the retrospective nature of our study, we acknowledge that other underlying clinical confounding factors or comorbidities might have contributed to these fatal outcomes; however, no other primary or definitive cause of death could be identified during the acute episode. A *Chi*-square test was applied to determine the connection between microorganisms and mortality, and no significant connection was found between them ($P>0.05$). The mortality rates within each bacterium are presented in Table 5.

4. Discussion

Numerous studies on Gram-negative bloodstream infections are available in the literature. In this study, we specifically focused on rare Gram-negative bacteria. The literature reports prolonged hospital stays due to Gram-negative infections. A multi-center cohort study found that the mean hospital stay after Gram-negative bacteremia in pediatric patients was (72±88) days, with most patients requiring treatments longer than 14 days[11]. Another study observed that the average hospital stay for children with non-fermentative Gram-negative bacterial infections was (97.9±177.5) days[12]. Similarly, single-center studies have reported that Gram-negative bloodstream infections lead to significantly prolonged hospitalizations[13]. These extended hospital stays further increase the risk of infection, particularly in pediatric patients in intensive care units, due to increased use of invasive devices[14]. In our patients, the average hospital stay was similarly determined to be 43.92 days.

Numerous risk factors have been reported for the development of Gram-negative bloodstream infections, including immunosuppression, premature birth and low birth weight, chronic diseases, invasive device use, intensive care unit admission, and total parenteral nutrition[15–19]. In our study, 94.0% of the enrolled patients had underlying chronic diseases, and the most common risk factors were catheter and blood product use. Furthermore, many of our patients had undergone cardiac surgery due to congenital heart disease. In children with congenital heart disease or after cardiac surgery, an increased susceptibility to infections, particularly pulmonary infections and sepsis, has been observed[20]. This can be

explained by the prolonged hospitalizations and frequent exposure to invasive procedures in patients with cardiac anomalies[20]. Infections observed in populations with underlying diseases are often caused by multidrug-resistant Gram-negative bacteria, which severely limits treatment options[21]. Therefore, early diagnosis of infection and rapid initiation of effective empirical treatment are critically important in these high-risk groups to prevent adverse clinical outcomes[13-22]. Additionally, meticulous application of prophylactic strategies and catheter care protocols in such patients can play a significant role in reducing the incidence of infection[2].

Each center may have different predominant microorganisms, and knowing their own microorganism profiles will facilitate empirical treatment. In our study, we reviewed the literature regarding the prevalence of the 22 Gram-negative microorganisms we investigated. A study examining 143 community-acquired Gram-negative blood culture isolates in children younger than three years found *Salmonella* spp. 26.3%, *Moraxella catarrhalis* 11.9%, *Haemophilus influenzae* 2.1%, *Proteus mirabilis* 1.4%, *Brevundimonas* spp. 1.4%, *Comamonas* spp. 0.7%, and *Sphingomonas* spp. 0.7%[23]. In an article investigating pediatric bloodstream infections caused by Gram-negative bacteria, 34 out of 327 isolates (10%) were *Enterobacter* spp.[24]. Another study examining pediatric bloodstream infections found that among 1 512 Gram-negative bacteria, *Stenotrophomonas maltophilia* (n=204, 13.5%), *Enterobacter* spp. (n=164, 10.8%), *Serratia marcescens* (n=121, 8%), and other microorganisms (*Klebsiella* spp, *Salmonella* spp, *Morganella morganii*, *Burkholderia cepacia*, *Haemophilus* spp, *Citrobacter freundii*, *Brucella* spp., *Proteus mirabilis*, *Neisseria meningitidis*) (n=157, 10.5%)[25]. Similarly, in our study, *Serratia* spp., *Stenotrophomonas maltophilia*, and *Enterobacter* spp. were frequently observed. Detailed analysis of the resistance profiles of these bacteria is critically important for identifying serious mechanisms, particularly carbapenem resistance, and thus for determining appropriate treatment strategies[3,26]. Particularly, *Stenotrophomonas maltophilia* stands out as a significant pathogen frequently encountered in immunocompromised patients and intensive care units, intrinsically resistant to many antibiotics and limiting treatment options 15. *Enterobacter* spp. can also develop inducible or permanent resistance mechanisms, especially against third-generation cephalosporins, leading to treatment failures. The presence of extended-spectrum beta-lactamases is directly related to resistance to third-generation cephalosporins[24]. *Serratia* spp., on the other hand, are generally environmental in origin and can cause serious infections as opportunistic pathogens in immunocompromised children[27]. These microorganisms, generally associated with nosocomial infections and prone to developing multidrug resistance, are playing an increasing role in pediatric bloodstream infections[28]. In our study, the intrinsic resistance of some rare Gram-negative pathogens to certain antibiotics complicated the selection of empirical treatment. Intrinsic resistance is a characteristic inherent in the genetic makeup of the bacterium and observed in all members of the species; unlike acquired resistance, it does not develop through antibiotic exposure[29]. Our findings support these natural resistance patterns. All 79 *Serratia* spp. isolates (100%) in our study were found to be resistant to trimethoprim/sulfamethoxazole, and 73 (92.4%) were resistant to colistin. These high resistance rates confirm the known natural resistance of *Serratia* spp. to colistin in the literature. Furthermore, a wide variability in susceptibility to imipenem and levofloxacin (3%-100% and 0%-73%, respectively) has been observed in the literature[30]. In our study, *Serratia* spp. did not show high resistance rates to these antibiotics, with observed rates of 20.2% and 3.7%, respectively. *Elizabethkingia meningoseptica* is known to be intrinsically resistant to carbapenems (meropenem, imipenem), aminoglycosides, and many beta-lactam antibiotics[31]. Our findings strongly support this natural resistance profile, as 5 out of 6 isolates (83.3%) were resistant to meropenem, imipenem, amikacin, piperacillin/tazobactam, and cefepime. All *Chryseobacterium* spp. isolates (100%) in our study were found to be resistant to meropenem, and 9 (90%) were resistant to imipenem, amikacin, and gentamicin. The literature indicates that *Chryseobacterium* species are known to exhibit natural resistance to a wide range of beta-lactam antibiotics and aminoglycosides[32]. Certain *Enterobacterales* species, such as *Serratia marcescens*, *Morganella morganii*, *Proteus mirabilis*, and *Burkholderia* spp., are intrinsically resistant to colistin due to the constitutive expression of genes leading to lipopolysaccharide modification[33]. In our findings, the resistance of *Morganella morganii* (3/3 isolates) and *Proteus mirabilis* (4/7 isolates) to colistin reflects these natural resistance patterns. In our study, 12 out of 16 *Burkholderia* spp. isolates (75%) were found to be resistant to colistin, 8 (50%) to imipenem, and 11 (68.8%) to cefepime. The literature states that *Burkholderia* spp. is a group of bacteria with multi-antimicrobial resistance[34]. *Stenotrophomonas maltophilia* has a broad spectrum of intrinsic resistance to many beta-lactams (especially carbapenems), aminoglycosides, and fluoroquinolones[35]. Therefore, trimethoprim/sulfamethoxazole is considered the first choice for the treatment of *Stenotrophomonas maltophilia* infections[36]. In our study, 81.1% of the isolated *Stenotrophomonas maltophilia* strains were found to be susceptible to co-trimoxazole, a rate that has been similarly reported in other studies in the literature. In patients suspected of healthcare-

associated infections, treatments covering *Stenotrophomonas maltophilia* must definitely be kept in mind[37].

It is well-established in the literature that carbapenem resistance among Gram-negative bacteria has been increasing over the years[22,26]. It has been determined that hospital stays exceeding 21 days significantly increase the risk of infection with carbapenem-resistant strains[3]. In our study, the meropenem resistance trend exhibited a fluctuating but generally upward trajectory between 2016 and 2023 (Figure 2). The record increase of 8.9% observed in 2021 is consistent with global reports of escalating antimicrobial resistance. We believe this sharp rise is closely linked to the clinical characteristics and treatment processes of our patient population.

Mortality was observed in 54 out of a total of 394 patients. Bacteria associated with sepsis-related mortality were *Aeromonas* spp., *Comamonas testosteroni*, and *Enterobacter* spp. The mortality rates of bloodstream infections caused by Gram-negative bacteria are at alarming levels due to the complexity of resistance profiles and limited treatment options[13]. Particularly, less common Gram-negative species, such as non-fermentative Gram-negative bacteria, are associated with high resistance rates and severe morbidity and mortality. The literature on these types of infections in children is more limited compared to adult data[38]. NFGNB are common in hospital settings and pose a risk for immunocompromised patients (oncological or hematological patients) or critically ill intubated patients[39]. Treating bacteremia caused by carbapenem-resistant NFGNB is a major challenge for clinicians[34]. Factors such as age, the patient's critical condition, recent antibiotic treatment, or contact with the healthcare system can contribute to clinical failure[39]. Generally, Gram-negative bloodstream infections are known to be associated with significant morbidity and mortality in children. Despite advances in medical care, mortality associated with pediatric bloodstream infections remains a concerning issue[13]. Multidrug-resistant Gram-negative bacteria pose a growing problem in pediatric patients, resulting in increased morbidity, mortality, and length of hospital stay, and the limited effective treatment options create a serious challenge for treatment and infection control[11]. Antimicrobial resistance trends, including the increasing prevalence of resistance to first-line antibiotics, lead to inadequate antibiotic therapy and mortality[40].

The management of bloodstream infections caused by rare Gram-negative bacteria in pediatric patients presents significant challenges due to complex resistance profiles and limited treatment options. Given the frequency and mortality associated with these infections, a detailed analysis of risk factors and the development of effective antimicrobial strategies are critically important for improving clinical practice. The results of our study provide valuable data for understanding the spread of resistant strains causing rare Gram-negative bacteremia in pediatric patients and the clinical outcomes associated with them. The resistance profiles obtained are a fundamental step for reviewing empirical treatment protocols and developing strategies to prevent the development of resistance, and will contribute to strengthening infection control measures and identifying targeted antimicrobial therapies.

The retrospective nature of this study and the data obtained from a single center may limit the generalizability of the results. Future multi-center prospective studies can address this limitation by providing more comprehensive and comparable data on the epidemiology of rare Gram-negative bacteremia in the pediatric population. Additionally, the lack of detailed data on previously used antibiotic treatments in some cases may affect the interpretation of the obtained antibiotic resistance profiles.

Conflicting interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

F.K. contributed to the conception, design, literature search, data analysis, statistical analysis, manuscript preparation and review. Ü.Ç. participated in the study design and manuscript editing. D.A. was responsible for the definition of intellectual content. Ö.Ö.G. conducted the literature search. F.T.Ç. acquired the experimental data. A.Ü. and N.N.T. assisted in manuscript preparation.

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