Original Investigation / *Özgün Araştırma*

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Evaluation of the Characteristics of *Citrobacter* spp. Bloodstream Infections in Pediatric Patients

Çocuk Hastalarda *Citrobacter* spp. Kan Dolaşım Yolu Enfeksiyonlarının Özelliklerinin Değerlendirilmesi

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Abstract

Objective: *Citrobacter* spp. is a gram-negative bacterium from the *Enterobacteriaceae* family that is an opportunistic pathogen causing infections such as urinary tract, respiratory tract, surgical wounds and bacteremia. Although *Citrobacter* strains colonizing the human gastrointestinal tract are traditionally thought to have low virulence, they can cause serious clinical pictures, especially in immunocompromised, neonatal and elderly groups. In recent years, it has been shown that the association with mortality is higher with the spread of multidrug resistant strains. In Türkiye, studies evaluating the characteristics of bloodstream infections caused by *Citrobacter* spp. in pediatric patients are rare. The aim of our study was to determine the clinical and laboratory findings, antibiotic resistance, mortality rate and prognosis of hospitalized patients with *Citrobacter* spp. in blood culture samples.

Material and Methods: Patients hospitalized in a tertiary care hospital between December 2013 and April 2021 with *Citrobacter* spp. growth in blood cultures were included in this study. Age, sex, comorbidities, presence of central venous catheter, use of mechanical ventilation, total parenteral nutrition, laboratory findings, duration of hospitalization, other sterile field culture samples, culture antibiograms, and antimicrobial treatments were determined as variables and recorded on pre-prepared forms.

Öz

Giriş: *Citrobacter* spp., *Enterobacteriaceae* ailesinden, fırsatçı bir patojen olarak idrar yolu, solunum yolu, cerrahi yaralar ve bakteriyemi gibi enfeksiyonlara neden olan gram negatif bir bakteridir. İnsan gastrointestinal sistemini kolonize eden *Citrobacter* suşlarının geleneksel olarak düşük virülansa sahip olduğu düşünülse de özellikle immün sistemi baskılanmış kişilerde, yenidoğan ve ileri yaş grubunda ciddi klinik tablolara neden olabilir. Son yıllarda çoklu ilaç dirençli suşlarının yaygınlaşmasıyla mortalite ile ilişkisinin daha yüksek olduğu gösterilmiştir. Türkiye'de çocuk hastalarda *Citrobacter* spp. kaynaklı kan dolaşım yolu enfeksiyonlarının özelliklerini değerlendiren çalışmalar nadirdir. Çalışmamızın amacı, hastanede izlenen ve kan kültür örneklerinde *Citrobacter* spp. üreyen olguların klinik ve laboratuvar bulguları ile antibiyotik direncinin belirlenmesi, mortalite oranı ve prognozun saptanmasıdır.

Gereç ve Yöntemler: Bu çalışmaya, üçüncü basamak bir hastanede Aralık 2013-Nisan 2021 tarihleri arasında yatan ve kan kültürlerinde *Citrobacter* spp. üremesi olan hastalar alınmıştır. Yaş, cinsiyet, eşlik eden hastalıklar, santral venöz kateter varlığı, mekanik ventilasyon kullanımı, total parenteral beslenme, laboratuvar bulguları, hastanede yatış süresi, diğer alınan steril alan kültür örnekleri, kültür antibiyogramları, verilen antimikrobiyal tedaviler değişkenler olarak belirlenerek, önceden hazırlanmış formlara kaydedildi.

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Results: Median age of the nine patients evaluated in the study was four months (min. 10 days-max. 30 months). Two (22.2%) of the patients were males and 7 (77.8%) were females. The most common reason for hospitalization was bronchopneumonia (n= 3, 33.3%). Six (66.6%) patients with *Citrobacter* spp. growth were intubated. Of the *Citrobacter* spp. growths, 44.4% (n= 4) were *Citrobacter freundii*, 22.2% (n= 2) were *Citrobacter koseri*, 22.2% (n= 2) were *Citrobacter werkmanii* and 11.1% (n= 1) were *Citrobacter farmeri*. Although all patients had growth in peripheral blood cultures, 44.4% (n= 4) had growth in central venous catheters, 11.1% (n= 1) had growth in intra-abdominal samples and 11.1% (n= 1) had growth in cerebrospinal fluid cultures. Eight (88.8%) of the *Citrobacter* species were extended spectrum beta-lactamase positive and two patients (22.2%) had carbapenem resistance. Thirty-day mortality rate was 11.1% (n= 1).

Conclusion: In patients in whom *Citrobacter* species are isolated, it is important to correctly evaluate this microorganism as a colonization, contamination or infection agent, make an early diagnosis and start appropriate treatment.

Keywords: *Citrobacter* spp., child, bloodstream infection

Bulgular: Çalışmada değerlendirilen dokuz hastanın ortanca yaşı dört ay (min. 10 gün-maks. 30 ay) idi. Hastaların 2 (%22.2)'si erkek, 7 (%77.8)'si kızdı. En sık yatış nedeni bronkopnömoni (n= 3, %33.3) idi. *Citrobacter* spp. üremesi olan 6 (%66.6) hastanın entübe şekilde izlendiği görüldü. *Citrobacter* spp. üremelerinin %44.4'ü (n= 4) *Citrobacter freundii*, %22.2'si (n= 2) *Citrobacter koseri*, %22.2'si (n= 2) *Citrobacter werkmanii* ve %11.1'i (n= 1) *Citrobacter farmeri* idi. Hastaların tümünde periferik kan kültüründe üreme olmakla beraber, eş zamanlı %44.4'ünde (n= 4) santral venöz kateterde, %11.1'inde (n= 1) batın içi alınan örnekte ve %11.1'inde (n= 1) beyin omurilik sıvı kültüründe de üreme saptandı. *Citrobacter* türlerinin 8 (%88.8)'inde genişlemiş spektrumlu beta-laktamaz pozitif olduğu ve ayrıca iki hastada (22.2%) karbapenem direnci olduğu görüldü. Hastalardaki 30 günlük mortalite oranı %11.1 (n= 1) olarak gözlemlendi.

Sonuç: *Citrobacter* türlerinin izole edildiği hastalarda, bu mikroorganizmanın kolonizasyon, kontaminasyon veya enfeksiyon etkeni olarak doğru bir şekilde değerlendirilmesi, erken tanı konulması ve uygun tedaviye başlanması önemlidir.

Anahtar Kelimeler: *Citrobacter* spp., çocuk, kan dolaşım yolu enfeksiyonu

Introduction

Citrobacter spp. are anaerobic, gram-negative bacilli from the *Enterobacteriaceae* family. *Citrobacter* strains can be found in environments such as water, soil, food, and in the gastrointestinal tract of animals and humans (1). Of the 11 identified strains of *Citrobacter*, three species, *Citrobacter freundii, Citrobacter koseri and Citrobacter farmeri*, have been isolated most frequently as the causative agents of infection in humans (1,2). *Citrobacter* infection is rare, and it constitutes 0.8% of all gram-negative infections and 3-6% of all *Enterobacteriaceae* isolates in healthcare-associated infections (3). It has been shown to cause infections with high mortality and morbidity in immunocompromised individuals, neonates and patients over 65 years of age. *Citrobacter* infections, which can frequently cause infections such as bacteremia, meningitis, central nervous system abscess, pneumonia, lung abscess, surgical site infections (especially intra-abdominal), diarrhea, osteomyelitis, septic arthritis in risky groups, have become an important health problem by developing multidrug resistance to antibiotics (4). In Türkiye, studies evaluating the characteristics of bloodstream tract infections caused by *Citrobacter spp*. in pediatric patients are rare and there is no data on the frequency in Türkiye. The aim of our study was to determine the clinical and laboratory characteristics, antibiotic resistance, mortality rate and prognosis in pediatric patients who were hospitalized and followed up and from whom *Citrobacter* strains were isolated in blood cultures.

Materials and Methods

Study Group

In this study, the medical records of patients aged 0-18 years with *Citrobacter* spp. growth in peripheral blood cultures who were hospitalized in a tertiary education and research hospital between December 2013 and April 2021 were retrospectively analyzed.

Data Collection

Patient files were reviewed for age, sex, comorbidities, presence of central venous catheter (CVC), use of mechanical ventilation, use of total parenteral nutrition (TPN), laboratory findings [white blood cell count, hemoglobin value, platelet count, C-reactive protein (CRP)], and length of hospitalization, peripheral blood culture and other sterile field culture samples (central venous catheter blood culture, cerebrospinal fluid culture, closed cavity fluid culture), culture antibiograms, antimicrobial treatments given, prognosis and 30-day mortality rate were recorded retrospectively. Healthcare-associated infection was defined as a localized or systemic infection that could not be detected at the time of initial admission and occurred on or after the 3rd day of hospitalization (5). Neutropenia was defined as absolute neutrophil count (ANC) $<1.5x10^9$/L, thrombocytopenia as platelet count $<150x10^9$/L and elevated CRP >0.5 mg/dL. Multidrug resistance (MDR) was defined as resistance to at least one antibiotic from three or more different classes (6). Blood cultures were obtained from the peripheral vein in a volume appropriate for the patient's age and weight (at least 1 ml) and from the peripheral vein and simultaneously (from the CVC, if available) in accordance with the rules of asepsis/antisepsis after personal protective measures were taken and inoculated into blood culture bottles at the bedside under asepsis conditions. *Citrobacter* spp. bacteremia was defined as the growth of *Citrobacter* spp. in at least one peripheral blood culture in a patient with compatible clinical findings. The diagnosis of catheter-related bloodstream tract infection (CRBSI) was made in accordance with the literature (7).

Microbiological Method

Samples obtained from the patients under appropriate conditions were inoculated on the surface of 5% sheep blood agar and eosin methylene blue (EMB) chocolate agar media using sterile pellets. The media plates were incubated in an incubator at 37°C for 18-24 hours in an aerobic environment

and 48 hours in an anaerobic environment and cultures with growth were examined. The first one of the recurrent growths in the same specimens of the patients was included in the study. Identification of the isolates and antimicrobial susceptibility tests were performed by conventional methods and VITEK 2 Compact (bioMérieux, Marcy l'Etoile, France) automated system. Antimicrobial susceptibility results were analyzed according to the Clinical and Laboratory Standards Institute (CLSI) until January 2017 (8). Afterwards, they were evaluated in accordance with the recommendations of The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Strains found to be susceptible "intermediate" at increased dose were considered resistant (9).

Statistical Analysis

SPSS Statistics, version 22 (SPSS Inc, Chicago, IL, USA) statistical program was used for statistical analysis of the data. Descriptive statistics were shown as mean ± standard deviation, median, minimum and maximum value for continuous variables and number and percentage for categorical variables.

Ethics committee permission was obtained from the Clinical Research Ethics Committee of our hospital for the study with decision number 158 and protocol number 857 dated 25.05.2023. The study was conducted in accordance with the principles of the Declaration of Helsinki and the principles described in good clinical practice and in compliance with the law.

Results

Demographic and Clinical Characteristics

Two (22.2%) of the patients were males and 7 (78.7%) were females. Median age of the patients was four months (min. 10 days-max. 30 months). The most common reason for hospitalization was bronchopneumonia (33.3%). All but two of the patients had at least one or more comorbidities. The most common comorbidity was down syndrome and cardiopathy (atrioventricular septal defect) (n= 2, 22.2%). *Citrobacter* spp. growth was detected in blood cultures taken on the mean 18.4th day of hospitalization (min. 0-max. 53 days). The growth of 7 (77.7%) patients was considered as healthcare associated infection. The most common hospitalization service (n= 4, 44.4%) was the pediatric intensive care unit. 44.4% (n= 4) of the patients had central venous catheters. Two had subclavian vein catheters, one had an internal jugular vein catheter, and the other patient had a port catheter. Six (66.6%) of the patients were receiving TPN support and the duration of TPN in these patients was between four and 105 days, except for one patient in whom the duration of TPN was at least 15 days. It was observed that 6 (66.6%) patients with *Citrobacter* spp. growth were intubated. Demographic characteristics of the patients are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the patients

Male, n (%)	2 (22.2%)
Female, n (%)	7 (77.8%)
Age (median)	4 month (10 days-30 month)
Reason for hospitalization, n (%)	
Bronchopneumonia	3 (33.3%)
Status epilepticus	1 (11.1%)
Intestinal atresia	1 (11.1%)
Myositis	1 (11.1%)
Colon perforation	1 (11.1%)
Acute gastroenteritis	1 (11.1%)
Late neonatal sepsis	1 (11.1%)
Underlying diseases, n (%)	
Down sendrom ve cardiopathy	2 (22.2%)
Prematurity and neurometabolic disease	1 (11.1%)
Intestinal atresia	1 (11.1%)
Duchenne mucular distrophy	1 (11.1%)
Congenital diarrhea	1 (11.1%)
Colon perforation	1 (11.1%)
None	2 (22.2%)
Wards, n (%)	
Pediatric infectious diseases	1 (11.1%)
Pediatric intensive care unit	4 (44.4%)
Pediatric surgery intensive care unit	2 (22.2%)
Neonatal intensive care unit	2 (22.2%)
Clinical characteristics, n (%)	
Central venous catheter	4 (44.4%)
Subclavian vein catheter	2 (22.2%)
Internal jugular vein catheter	1 (11.1%)
Port catheter	1 (11.1%)
TPN	6 (66.6%)
Intubation	6 (66.6%)
Symptom and findings, n (%)	
Fever	6 (66.6%)
Tachycardia	2 (22.2%)
Tachypnea	2 (22.2%)
Hipotension	3 (33.3%)
Cyanosis	1 (11.1%)
Vomiting	2 (22.2%)
Diarrhea	2 (22.2%)
Abdominal distention	2 (22.2%)
Bulging fontanelle	1 (11.1%)
Citrobacter species, n (%)	
C. freundii	4 (44.4%)
C. koseri	2 (22.2%)
C. werkmanii	2 (22.2%)
C. farmeri	1 (11.1%)

TPN: Total parenteral nutrition.

Findings Associated with *Citrobacter* spp. Infection

A total of nine patients with *Citrobacter* spp. related bloodstream tract infections were detected during the study period. Of the *Citrobacter* spp. growths, 44.4% (n= 4) were *C. freundii*, 22.2% (n= 2) were *C. koseri*, 22.2% (n= 2) were *Citrobacter werkmanii* and 11.1% (n= 1) were *C. farmeri*. Although all patients had growth in peripheral blood cultures, 44.4% (n= 4) had growth in central venous catheter samples, 11.1% (n= 1) had growth in intra-abdominal samples and 11.1% (n= 1) had growth in cerebrospinal fluid cultures. No other growths other than *Citrobacter* spp. were detected in the cases. Among the patients with *Citrobacter* spp. growth, 6 (66.6%) had fever, 3 (33.3%) had hypotension, 2 (22.2%) had tachypnea, 2 (22.2%) had tachycardia and 2 (22.2%) had diarrhea. Clinical findings of the patients are summarized in Table 2. In patients with *Citrobacter* spp. growth, white blood cell count was 7806.7 ± 4753.0 x10^9/L (700-16500 x10^9/L), hemoglobin was 10.2 ± 1.6 g/dL (8.3-13.2 g/dL), platelet count was 233355 ± 161968 x10^9/L (11200-475000 x10^9/L), CRP was 79. 8 ± 42.4 mg/dL (6.4-123.0 mg/dL). Neutropenia was detected in 1 (11.1%) and thrombocytopenia in 3 (33.3%) patients.

Antimicrobial Susceptibility Results of *Citrobacter* spp.

It was observed that 8 (88.8%) of *Citrobacter* species were extended spectrum beta-lactamase positive and 2 (22.2%) patients had carbapenem resistance. Amikacin resistance was found in 33.3% (n= 3), gentamicin resistance in 33.3% (n= 3), trimethoprim/sulfamethoxazole resistance in 44.4% (n= 4) and piperacillin/tazobactam resistance in 5.6% (n= 5) of the isolates. Tigecycline resistance was detected in one of the five isolates tested (20%). Meropenem resistance was detected in 22.2% (n= 1). Ciprofloxacin resistance was not detected. Antimicrobial treatment and prognosis of the patients Although the treatments of the patients varied, five patients received meropenem, one patient received cefotaxime and gentamicin combination, one patient received colistin and amikacin combination, one patient received piperacillin/tazobactam and amikacin combination, and one patient received ciprofloxacin. Patients were treated for periods ranging between 14-21 days depending on their clinical conditions. The patient diagnosed with meningoencephalitis and brain abscess was referred to a neurosurgical center on the 4th day of meropenem and amikacin combination treatment. The clinical characteristics of the patients and the antibiotic treatment and duration of antibiotic treatment after growth are given in Table 2. One of the patients had multiple brain abscess foci and cerebrospinal fluid culture of this patient showed growth of *C. koseri* (Figure 1). The 30-day mortality rate was 11.1% (n= 1). Mitochondrial cytopathy was present in the patient with mortality.

Table 2. Clinical characteristics, treatment and prognosis of the patients with *Citrobacter* spp. bloodstream tract infections

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (months)	6	30	29 days	11	43	10 days	4	9	14 days
Sex	F	F	F	M	F	F	F	F	M
Underlying disease/ Reason for hospitalization	Down syndrome and AVSD/ Bronchopneumonia	PM and NMD/ Status epilepticus	Intestinal atresia/ Intestinal atresia	Duchenne muscular dystrophy/ Myositis	Congenital diarrhea/ Acute gastroenteritis	None/Late neonatal sepsis	Mitochondrial cytopathy/ Bronchopneumonia	Down sendrom and AVSD/ Bronchopneumonia	None/Colon perforation
Growth site	Peripheral blood and catheter	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood and catheter	Periferik kan and CSF	Peripheral blood and catheter	Peripheral blood and catheter	Peripheral blood and intra-abdominal fluid
Agent	*C. farmeri*	*C. freundii*	*C. freundii*	*C. werkmanii*	*C. koseri*	*C. koseri*	*C. werkmanii*	*C. freundii*	*C. freundii*
Antibiogram result	ESBL positive	Carbapenem-resistant	ESBL positive	ESBL negative	ESBL positive	ESBL positive	ESBL positive	Carbapenem-resistant	ESBL positive
Antibiotic treatment (day)	Piperacillin taxobactam (24)+amicasin (10)	Amikacin (10)+cholistin (21)	Meropenem (16)	Cefotaxime (15)+gentamicin (7)	Meropenem (21)	Meropenem (4)+amikacin (4)	Meropenem (20)	Piperacillin taxobactam (5)+ciprophloxacin (12)	Meropenem (14)
Prognosis	Discharged	Discharged	Discharged	Discharged	Discharged	Day 5 referral to an external center	Exitus	Discharged	Discharged

F: Female, M: Male, PM: Prematurity, NMD: Neurometabolic disease, SSBL: Extended spectrum beta-lactamase, CSF: Cerebro-spinal fluid, AVSD: Atrioventricular septal defect.

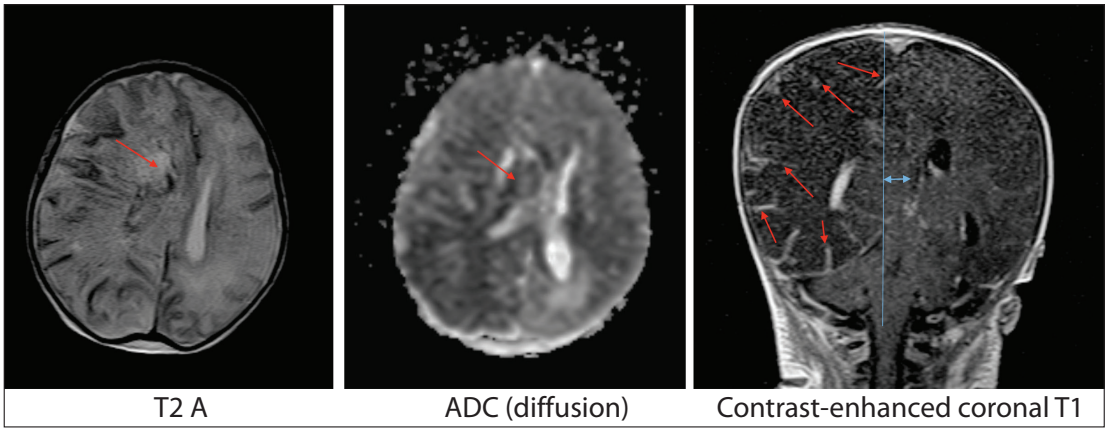

Figure 1. Cranial magnetic resonance imaging of a patient with multiple brain abscess foci due to *C. koseri* growth. T2 A and diffusion (ADC) images show diffusion restriction within the abscess (red arrows). Diffusion restriction supports the abscess. Contrast enhancement shows diffuse pachymeningeal contrast enhancement (red arrows), edema in the right cerebral parenchyma and midline shift (blue arrow). Findings suggest cerebritis+brain edema and meningitis on the right (meningoencephalitis).

Discussion

In our study, demographic characteristics, clinical and laboratory findings, antibiotic susceptibility rates and their relationship with morbidity and mortality were retrospectively evaluated in nine patients with *Citrobacter* spp. infection. Most of our patients were followed up in the intensive care unit, and *Citrobacter* bacteremia was detected in all cases, and 44.4% of them had *C. freundii* growth. In addition, 88.8% of the patients were extended spectrum beta-lactamase positive, 22.2% had carbapenem resistance, 55.6% had piperacillin/tazobactam resistance, 33.3% had amikacin resistance and no ciprofloxacin resistance was detected. 30-day mortality was calculated as 11.1%.

It is known that *Citrobacter* spp. can cause serious infections, especially in newborns (NICU), adults over 65 years of age, diabetics and immunocompromised individuals (10,11). In our study, 8 (88.8%) of the cases were hospitalized in the intensive care unit, 2 (22.2%) were in the neonatal intensive care unit and 2 (22.2%) had down syndrome, and there were no cases with immunosuppressive diagnosis. In general, growth of *Citrobacter* spp. in blood cultures obtained from hospitalized patients has been reported as 0.5% in studies and is a rare cause of bacteremia (12). *Citrobacter* spp. infections are frequently nosocomial in origin, are seen in patients with comorbidities and generally *Citrobacter* species are resistant to antimicrobial drugs (1,3,6,14). In Türkiye, the number of studies evaluating bloodstream infections caused by *Citrobacter* spp. in pediatric patients is quite limited (13). Mohanty et al. reported that 88.3% of a total of 205 patients from whom *Citrobacter* spp. were isolated in inpatients and outpatients, ranging from three days NICU to 87 years of age, had underlying diseases and 94.6% of the patients were healthcare related (14). In our study, although the sample size was small, it was found to be a healthcare-associated infection in the majority of cases (n= 7, 77.7%) in accordance with the literature.

In a study conducted by Brenner et al. to determine the genetic relatedness of 112 strains, 11 strains including *Citrobacter amalonaticus, C. freundii, C. koseri, C. werkmanii, C. farmeri, Citrobacter braakii, Citrobacter gillenii*, etc. were identified and it was reported that *C. freundii* and *Citrobacter youngae* were pathogenic for humans (15). When we look at the isolated species in our study, *C. freundii* was the most common with 44.4% and *C. koseri* was the second most common with 22.2%. In studies, *C. koseri*, which is the most frequently encountered species especially in neonatal meningitis, has been shown to be associated with meningitis, ventriculitis, multiple abscess formation in the brain and mortality due to its resistance to intraphagocytic killing with an outer membrane protein with a molecular weight of 32.000 kDa (16,17). In our study, *C. koseri* was found in a case with neonatal brain abscess. In a retrospective study by Samonis et al. in which 70 adult patients were evaluated for 12 years, the most common *Citrobacter* species was *C. freundii* (71.8%) (18). This was followed by *C. koseri* (23.1%) and *C. braakii* (3.8%). The most common associated source of infection in their study was urinary tract infection (52.6%), intra-abdominal (14.1%), surgical site (7.7%), skin and soft tissue (6.4%) and respiratory tract infections (6.4%). *Citrobacter* spp. is known to cause urinary tract infections in adults and rarely urinary tract infections in children (19). In our study, the most common reason for hospitalization in the pediatric age group was bronchopneumonia, which was the most common primary source of bacteremia.

Antibiotic resistance observed in *Citrobacter* species shows a wide spectrum. These low virulence bacteria, which were initially considered as contamination and/or colonization, have gradually developed resistance with the effect of antibiotic use over time. Especially the emergence of multidrug-resistant *Cit-*

robacter species is a growing concern (20). Multidrug-resistant *C. freundii* strains have been associated with a higher hospital mortality rate compared to susceptible strains (21). The frequent isolation of *C. freundii* resistant to β-lactams, quinolones and aminoglycosides has been reported by various international surveillance programs (22). In cases with long-term hospitalization and comorbidities, appropriate antibiotic treatments together with infection control measures are important for the prevention of drug-resistant strains against *Citrobacter* species (23). In our study, 88.8% of *Citrobacter* species were extended spectrum beta-lactamase (ESBL) positive and 22.2% were carbapenem resistant, 33.3% were amikacin resistant and 33.3% were gentamicin resistant. Although our sample size was small, when we analyzed drug resistance according to *Citrobacter* species, half of the *C. freundii* cases (44.4%) were carbapenem resistant and the other half were ESBL positive. In addition, amikacin gentamicin resistance was observed in *C. freundii* cases with carbapenem resistance. Multidrug resistance was present only in *C. freundii* cases. In most of the previous studies, MDR *Citrobacter* strains were detected more frequently in patients who had received previous antibiotic treatment (24). In our study, 75% of the cases with multidrug resistance had a history of long-term hospitalization and multiple antibiotic use before the growth of *Citrobacter* spp. In a study published in 2019 and retrospectively evaluating cases with *Citrobacter* spp. growth, no significant difference was observed between *C. freundii* and non- *C. freundii* bacteremia in terms of clinical features and antimicrobial susceptibility rate (15). Although the prevalence of resistance of *Citrobacter* species to quinolone group drugs is gradually increasing in studies in the literature, the resistance rate of *C. freundii* to quinolones was found between 7.5% and 23.9% in one analysis (6,22). In our study, *Citrobacter* species were not resistant to the quinolone group.

In the treatment of *Citrobacter* infections, although there is no evidence to support the superiority of one antimicrobial treatment combination over the other, the combination of a third or fourth generation cephalosporin or carbapenem (usually meropenem) with an aminoglycoside has been recommended as initial treatment (1). Pharmacologic data have recently led to a recommendation to consider meropenem as the antimicrobial of choice for the treatment of *C. koseri* and *C. freundii* infections (1,25). In general, the recommendation is to direct the treatment with antimicrobial susceptibility testing. In our study, meropenem, ciprofloxacin, and third generation cephalosporin and aminoglycoside combination were preferred according to the culture antibiogram.

In the literature, the mortality rate in hospitalized patients with *Citrobacter* spp. infections was 6.8% and this rate increased significantly to 17.8-56% in *Citrobacter* bacteremia (24,26). In addition, multidrug-resistant *C. freundii* strains have been associated with a higher in-hospital mortality rate compared to other susceptible strains (21). In addition, risk factors associated with mortality in ESBL-producing *Citrobacter* infections include hospitalization in the pediatric intensive care unit, prolonged hospitalization, nosocomial infection, broad-spectrum antibiotic use, prolonged antibiotic use, immunosuppressive treatment, presence of chronic disease, thrombocytopenia and presence of central venous catheters (21,27). In our study, ESBL-producing *Citrobacter* spp. was grown in a patient in whom mortality was observed and risk factors such as prolonged hospitalization history, broad-spectrum antibiotic use, presence of central venous catheter and thrombocytopenia were present.

In addition to taking necessary precautions in hospital health practices such as environmental cleaning, isolation of infected patients and hand hygiene, optimal antibiotic selection and duration of use are of great importance in preventing bloodstream infections caused by *Citrobacter* spp. (28,29).

The most important limitations of our study include retrospective study, deficiencies in the records related to the clinical follow-up process, and the low number of cases. Multicenter prospective studies including more patient groups, multicenter prospective follow-up and records will benefit the literature and clinical follow-up.

Conclusion

Citrobacter strains, as opportunistic infection agents, may be the cause of mortality, especially in mature patients hospitalized in intensive care units. Early diagnosis of *Citrobacter* infection in this patient group, initiation of appropriate treatment and taking infection control measures are necessary to reduce drug-resistant strains as well as *Citrobacter* mortality.

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References

1. *Cherry J, Demmler-Harrison GJ, Kaplan, SL, SteinbachnWJ, Hotez PJ. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. Elsevier Health Sciences 2019, p.1020-24.*
2. *Frederiksen W. Citrobacter. Bergey's Manual of Systematics of Archaea and Bacteria, Wiley Online Library 2015, 1-23. https://doi.org/10.1002/9781118960608.gbm01143*
3. *Lavigne JP, Defez C, Bouziges N, Mahamat A, Sotto A. Clinical and molecular epidemiology of multidrug resistant Citrobacter spp. infections in a French university hospital. Eur J Clin Microbiol Infect Dis 2007;26:439-41. https://doi.org/10.1007/s10096-007-0315-3*
4. *Centers for Disease Control and Prevention (CDC). Vital signs: Carbapenem-resistant Enterobacteriaceae. MMWR Morb Mortal Wkly Rep 2013;62:165-70.*
5. *Centers for Disease Control and Prevention. Identifying Healthcare-associated Infections (HAI) for NHSN Surveillance criteria. Available from: https://www.cdc.gov/hai/infectiontypes.html (Accessed date 6.02.2024).*
6. *Liu L, Qin L, Hao S, Lan R, Xu B, Guo Y, et al. Lineage, Antimicrobial Resistance and Virulence of Citrobacter spp. Pathogens 2020;9:195. https://doi.org/10.3390/pathogens9030195*
7. *Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1-45. https://doi.org/10.1086/599376*
8. *CLSI. Performance Standards for Antimicrobial Susceptibility Testing. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.*
9. *EUCAST. Available from: https://www.eucast.org/clinical_breakpoints (Accessed date: 6.02.2024).*
10. *Borenshtein D, Schauer DB. The Genus Citrobacter. In: Dworkin M, Falkow S, Rosenberg E, Schleifer K-H, Stackebrandt E, editors. The Prokaryotes: A Handbook on the Biology of Bacteria Volume 6: Proteobacteria: Gamma Subclass. New York: Springer; 2006:90-8. https://doi.org/10.1007/0-387-30746-X_5*
11. *Aral M, Kireçci E, Doğan ŞS. İdrar örneklerinden izole edilen gram negatif bakteriler ve antibiyotiklere direnç oranlarının retrospektif olarak değerlendirilmesi. Türk Mikrobiyol Cem Derg 2011;41(4):139-42.*
12. *Pfaller MA, Jones RN, Marshall SA, Coffman S, Hollis RJ, Edmond MB, et al. Inducible amp C beta-lactamase producing gram-negative bacilli from blood stream infections: Frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE). Diagn Microbial Infect Dis 1997;28:211-19. https://doi.org/10.1016/S0732-8893(97)00064-3*
13. *Çalgın MK, Çetinkol Y. Evolation of antibotic resistance of Citrobacter strains isolated from variioud Clinical Samples in a University Hospital Between 2014-2018. Ankem Derg 2019;33:65-69. https://doi.org/10.5222/ankem.2019.1917*
14. *Mohanty S, Singhal R, Sood S, Dhawan B, Kapil A, Das BK. Citrobacter infections in a tertiary care hospital in Northern India. J Infect 2007;54:58-64. https://doi.org/10.1016/j.jinf.2006.01.015*
15. *Lee R, Choi SM, Jo SJ, Lee J, Cho SY, Kim SH, et al. Clinical characteristics and antimicrobial susceptibility trends in citrobacter bacteremia: An 11-Year single-center experience. Infect Chemother 2019;51:1-9. https://doi.org/10.3947/ic.2019.51.1.1*
16. *Kline MW, Kaplan SL, Hawkins EP, Mason EO Jr. Pathogenesis of brain abscess formation in an infant rat model of Citrobacter diversus bacteremia and meningitis. J Infect Dis 1988;157:106-12. https://doi.org/10.1093/infdis/157.1.106*
17. *Rodrigues J, Rocha D, Santos F, João A. Neonatal Citrobacter koseri Meningitis: Report of Four Cases. Case Rep Pediatr 2014;2014:195-204. https://doi.org/10.1155/2014/195204*
18. *Samonis G, Karageorgopoulos DE, Kofteridis DP, Matthaiou DK, Sidiropoulou V, Maraki S, et al. Citrobacter infections in a general hospital: characteristics and outcomes. Eur J Clin Microbiol Infect Dis 2009;28:61-8. https://doi.org/10.1007/s10096-008-0598-z*
19. *Gill MA, Schutze GE. Citrobacter urinary tract infections in children. Pediatr Infect Dis J 1999;18:889-92. https://doi.org/10.1097/00006454-199910000-00010*
20. *Khorasani, G, Salehifar E, Eslami, G. Profile of Microorganisms and Antimicrobial Resistance at a Tertiary Care Referral Burn Centre in Iran: Emergence of Citrobacter Freundii as a Common Microorganism 2008;34:947-52. https://doi.org/10.1016/j.burns.2007.12.008*
21. *Deal EN, Micek ST, Ritchie DJ, Reichley RM, Dunne WM, Kollef MH. Predictors of in-hospital mortality for bloodstream ınfections caused by enterobacter species or Citrobacter freundii. Pharmacotherapy 2007;27:191-9. https://doi.org/10.1592/phco.27.2.191*
22. *Oliveira H, Pinto G, Oliveira A, Oliveira C, Faustino MA, Briers Y. Characterization and genome sequencing of a Citrobacter freundii phage CfP1 harboring a lysin active against multidrug-resistant isolates. Appl Microbiol Biotechnol 2016;100:10543-53. https://doi.org/10.1007/s00253-016-7858-0*
23. *Liu L, Zhang L, Zhou H, Yuan M, Hu D, Wang Y, et al. Antimicrobial Resistance and Molecular Characterization of Citrobacter spp. Causing Extraintestinal Infections. Front Cell Infect Microbiol 2021;11:737636. https://doi.org/10.3389/fcimb.2021.737636*
24. *Liu LH, Wang NY, Wu AY, Lin CC, Lee CM, Liu CP. Citrobacter freundii bacteremia: Risk factors of mortality and prevalence of resistance genes. J Microbiol Immunol Infect 2018;51:565-72. https://doi.org/10.1016/j.jmii.2016.08.016*
25. *Sullivan KV, Deburger B, Roundtree SS, Ventrola CA, Blecker-Shelly DL, Mortensen JE. Pediatric multicenter evaluation of the Verigene gram-negative blood culture test for rapid detection of inpatient bacteremia involving gram-negative organisms, extended-spectrum beta-lactamases and carbapenemases. J Clin Microbial 2014;52:2416-21. https://doi.org/10.1128/JCM.00737-14*
26. *Gupta N, Yadav A, Choudhary U, Arora DR. Citrobacter bacteremia in a tertiary care hospital. Scand J Infect Dis 2003;35:765-8. https://doi.org/10.1080/00365540310016376*
27. *Deveci A, Coban AY. Optimum management of Citrobacter koseri infection. Expert Rev Anti Infect Ther 2014;12(9):1137-42. https://doi.org/10.1586/14787210.2014.944505*
28. *Sümer Ş, Kurt Azalp Ö, Aygün G, Akalın H, Akova A, Köksal İ. Dirençli gram-negatif bakteri infeksiyonlarının yönetiminde sık karşılaşılan sorunlar ve çözüm önerileri: Klinik pratiğe yönelik uzman görüşü. FLORA 2024;29(1):1-24. https://doi.org/10.5578/flora.2024011051*
29. *Fonton P, Hassoun-Kheir N, Harbarth S. Epidemiology of Citrobacter spp. infections among hospitalized patients: A systematic review and meta-analysis. BMC Infectious Diseases 2024;24(1):662. https://doi.org/10.1186/s12879-024-09575-8*