



Bloodstream Infections Caused by *Serratia marcescens*: Have a High Prevalence of ESBL and Carbapenemase Production in Pediatric Patients

Çocuk Hastalarda *Serratia marcescens* Bakteriyemisi:
Yüksek Oranda ESBL ve Karbapenemaz Üretimi

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Abstract

Objective: In this study, it was aimed to present a cohort study conducted retrospectively in order to examine the unexpected *Serratia marcescens* bacteremia prevalence in a children's hospital in Türkiye.

Material and Methods: *S. marcescens* was isolated in the blood cultures of 45 patients at a 20-month period. Demographic features and clinical findings of the 45 patients including age, sex, underlying diseases, white blood cell (WBC), C-reactive protein (CRP), serum albumin level, length of hospital stay and length of pediatric intensive care unit stay, portal of entry, duration of central venous catheter, results of antimicrobial susceptibility testing and 28-day all-cause mortality were examined. Bloodstream infections (BSI) were classified as BSI or catheter-related BSI. Definitions used to characterize antimicrobial resistant bacteria were classified as multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR).

Results: Twelve patients (26.9%) had a malignancy. Mean hospitalization duration was 42.7 ± 41.4 (3-171) days. Central venous catheters (CVCs), including chemo-ports and Hickman catheters, were present in 43 patients during episodes of BSI. Twenty-four patients had primary BSI while 21 patients had catheter-related BSI. Mean length of CVC presence be-

Öz

Giriş: Bu çalışmanın amacı, 20 aylık bir dönem içerisinde kan kültüründe *Serratia marcescens* üreyen hastalarda beklenmedik bir artış olması ile bu hastaların demografik, klinik ve laboratuvar sonuçlarının incelenmesi, mortaliteye yol açan özelliklerin ve dirençli suşlara tedavi yaklaşımının gözden geçirilmesidir.

Gereç ve Yöntemler: Kan kültüründe *S. marcescens* üreyen ve bakteriyemi ile uyumlu klinik bulguları olan hastalar geriye dönük olarak incelenmiştir. Yaş, cinsiyet, altta yatan hastalıklar, beyaz küre ve nötrofil sayıları, C-reaktif protein (CRP) ve albümin düzeyleri, hastanede yatış süresi, yoğun bakımda yatış süresi, santral venöz kateter varlığı ve süresi, 28-gün mortalitesi ve antibiyogram kaydedildi. Enfeksiyonlar kan yayım veya kateter ilişkili kan yayım enfeksiyonu olarak ayrıldı. Antimikrobiyal direnci değerlendirmek için suşlar non-MDR, MDR, XDR ve PDR olarak sınıflandırıldı.

Bulgular: Hastaların 12 (%26.9)'sinin altta yatan hastalığı maligniteydi. Ortalama hastanede kalış süresi 42.7 ± 41.4 (3-171) gündü. Kan yayım enfeksiyonları sırasında 43 hastada kemo-portlar ve Hickman kateterleri dahil santral venöz kateterler mevcuttu. Yirmi dört hastada kan yayım enfeksiyonu, 21 hastada kateterle ilişkili kan yayım enfeksiyonu mevcut-

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fore catheter-related BSI was 46.02 ± 50.96 (1-200) days. During bacteremia episodes, 24 catheters (55.8%) were removed. Four patients (8.9%) died during the bacteremia episode. Laboratory findings of the deceased patients were as follows: mean WBC was $17.200/\text{mm}^3$; mean serum CRP level was 147.2 mg/L; and mean serum albumin level was 2.43 g/dL. Among all cases, 57.8% of the *S. marcescens* isolates produced ESBL and 40% produced carbapenemase. We classified these isolates as non-MDR (42.2%), MDR (31.1%), XDR (24.4%) and PDR (2.2%). The most common regimes received for XDR isolates were high-dose prolonged meropenem, amikacin, levofloxacin, and tigecycline.

Conclusion: It is a great concern that *S. marcescens* isolates are intrinsically resistant to polymyxins and produce ESBL and carbapenemase. Our mortality rate was reduced by high-dose prolonged-infusion of meropenem and early catheter removal.

Keywords: ESBL, high-dose prolonged-infusion of meropenem, *S. marcescens*, pan-drug resistant

Introduction

Serratia species are opportunistic gram-negative bacteria classified in the *Enterobacteriaceae* family. *S. marcescens* is associated with severe and mortal nosocomial infections such as pneumonia, urinary and biliary tract infections, peritonitis, and intravenous catheter-related infections. *S. marcescens* can also be a significant nosocomial pathogen that might cause outbreaks (1-3). Epidemiologic data report that extended spectrum betalactamase (ESBL) and carbapenemase production is increasing in *S. marcescens* strains (4-6). Our study isolated *S. marcescens* strains with a high prevalence of ESBL and carbapenemase production within 20 months. *S. marcescens* bacteremia has a mortality rate varying between 25-58% (6-8). Our mortality rate was lower compared to that of other studies. Demographic and clinical characteristics of the patients, underlying diseases and treatment of the patients were recorded. The primary goal was to identify factors that were in correlation with *S. marcescens*-related mortality during the clustering period.

Materials and Methods

S. marcescens bacteremia features in a 270-bed children's hospital in Ankara, Türkiye were examined as a retrospective cohort study. *S. marcescens* was isolated in the blood cultures of 45 patients within 20 months. Inclusion criteria for this study were positive blood cultures for *S. marcescens* and the presence of clinical bacteremia findings. Patient demographics and clinical features including age, sex, underlying diseases, white blood cell (WBC), C-reactive protein (CRP), serum albumin level, hospitalization duration, length of pediatric intensive care unit stay (PICU) stay, the portal of entry, duration of the central venous catheter, antimicrobial susceptibility, and all-cause 28-day mortality were obtained from hospital medical data system.

tu. Kateterle ilişkili kan yayım enfeksiyonu öncesi santral venöz kateterin mevcut kalış süresi 46.02 ± 50.96 (1-200) gündü. Bakteriyemi atakları sırasında 24 kateter (%55.8) çekildi. Dört hasta (%8.9) bakteriyemi atağı sırasında kaybedildi. Kaybedilen hastaların laboratuvar bulguları şöyleydi; ortalama WBC $17.200/\text{mm}^3$; ortalama serum CRP seviyesi 147.2 mg/L idi; ortalama serum albümin düzeyi 2.43 g/dL idi. Tüm üremeler arasında *S. marcescens* izolatlarının %57.8'i ESBL, %40'ı ise karbapenemaz ürettiyordu. Bu izolatlar MDR olmayan (%42.2), MDR (%31.1), XDR (%24.4) ve PDR (%2.2) olarak sınıflandırıldı. XDR izolatları için kullanılan en yaygın antimikrobiyal rejimler yüksek doz uzun süreli meropenem, amikasin, levofloksasin ve tigesiklin idi.

Sonuç: *S. marcescens* önemli nosokomiyal etkenlerden biridir ve gide rek artan direnç paterni bildirilmektedir. *S. marcescens*'in polimiksinlere doğal dirençli olması ve bu çalışmada da saptandığı üzere ESBL ve karbapenemaz üretiminin artışı endişe vericidir. Tedavi başarısızlığı ve ölüm yüksek doz ve erken dönemde kateter çekilmesi ile azaltılabilir.

Anahtar Kelimeler: ESBL, yüksek doz uzun süreli meropenem infüzyonu, *S. marcescens*, çoklu ilaç direnç

Bloodstream infections (BSI) are classified as BSI or catheter-related BSI. Catheter-related BSI was considered in patients who had an intravascular device, >1 positive peripheral vein blood culture, clinical manifestations of infection in the absence of another apparent source for BSI. In order to identify a catheter-related BSI, a blood sample was taken from both the catheter and peripheral vein simultaneously, and culture growth was expected in the catheter culture at least two hours before peripheral blood culture (9).

Nosocomial BSI was defined as a positive blood culture obtained from patients who had been hospitalized for 48 hours or longer (10,11). Polymicrobial BSI was defined if more than one microorganism was identified in the same blood culture bottle.

Underlying diseases were defined under the international classification of diseases. The most common causes of hospitalization were hemato-oncological malignancy, cardiovascular diseases, prematurity, neuromuscular disease, and chronic lung diseases (12).

Identification of *S. marcescens* species was performed using conventional methods (BACTEC 9240, Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.). Species identification and antimicrobial susceptibility testing were performed in local laboratories in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST, <https://eucast.org>) or Clinical and Laboratory Standards Institute (CLSI, <https://clsi.org>) guidelines (13-15).

In recent years, multidrug-resistant *Enterobacteriaceae* isolates have been increasingly reported, and this resistance pattern and limited treatment options pose a great risk. Due to the increasing resistance pattern, the classification of resistant strains has been brought up. A group of international experts, including the European Centre for Disease Prevention and

Control and the Centers for Disease Control and Prevention, has created a standardized international terminology to describe acquired resistance profiles in bacteria. For the defined *Enterobacteriaceae*, aminoglycosides, anti-MRSA cephalosporins, antipseudomonal penicillins+beta-lactamase inhibitors, carbapenems, third and fourth generation cephalosporins, cephamycins, fluoroquinolones, trimethoprim-sulphamethoxazole, tigecycline, monobactams, chloramphenicol, and fosfomycin have been used, and multidrug-resistance (MDR) has been defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug-resistance (XDR) has been defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories, and pan-drug resistance (PDR) has been defined as non-susceptibility to all agents in all (16).

Since 45 positive *S. marcescens* blood cultures were reported within twenty months, a possible origin of cause for this clustering bacteremia was investigated. Hand cultures of medical staff and environmental samples were collected to determine carriers of *S. marcescens*. Twenty-three environmental samples were collected; fifteen were collected from the hands of medical staff nursing the patients. Furthermore, medical solutions, disinfectants, and taps were sampled for culture. All medical staff received training on preventing nosocomial infections.

The protocol for this retrospective study was approved by the ethics committee of a university medical school (Date: 26.02.2018, ethics committee approval number: 04-220-18). Data of the research was not used beyond scientific purposes.

Statistical Analysis

Continuous variables were presented with median, mean, standard deviation, minimum, and maximum values. The variables with normal distribution were evaluated with the Kolmogorov-Smirnov Test. Intergroups were analyzed with the Mann-Whitney U test and the Student's t-test. All data analyses were performed using SPSS Version SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Significance level was $p < 0.05$.

Results

Within twenty months, 45 *S. marcescens* BSI episodes were identified in 39 patients. BSI episodes with *S. marcescens* recurred at different times in six patients. The number of male patients was 24 (66.7%), and patients' median age was 13 months (min-max 1-198 months). Twenty-eight of the patients whose blood cultures were positive for *S. marcescens* were hospitalized in PICU, eight of them in the neonatal intensive care unit, six of them in the pediatric hematology-oncology ward, and three of them in the pediatric surgery department. Patient demographics, clinical characteristics, and most common underlying diseases are shown in the Table 1.

The most common underlying disease was malignancy, and hematological disorders (26.9%), followed by neuromuscular diseases (22.2%), prematurity (17.7%), cardiovascular diseases (13.3%). Of the patients, 64.4% needed mechanical ventilation, and 26.7% received total parenteral nutrition. Median hospitalization duration was 31 (3-171) days-80% of the patients presented with bacteremia during the intensive care unit stay. Forty-three patients had CVCs, including chemoports and Hickman catheters, during BSI episodes. Primary BSI was diagnosed in 24 (53.3%) episodes, catheter-related BSI was considered in 21 episodes. Median CVC duration before catheter-related BSI was 31 (1-200) days. During the bacteremia episode, 24 catheters (55.8%) were removed.

According to our study sample, mean WBC was $13.870 \pm 10.1/\text{mm}^3$ (min-max; 0.5-36.7/ mm^3); mean serum C-reactive protein (CRP) level was 124.7 ± 107.8 mg/L (min-max; 1-395 mg/L); and mean serum albumin level was 2.76 ± 0.62 g/dL (min-max; 1-4.1 g/dL). Four patients (8.9%) died during the bacteremia episode. Mean WBC was $17.200 \pm 14.79/\text{mm}^3$, mean serum CRP level was 147.2 ± 80.79 mg/L, and mean serum albumin level was 2.43 ± 0.23 g/dL in the fatal group.

In total, 45 blood cultures were positive for *S. marcescens*, and 17.8% (eight patients) of the BSI episode were polymicrobial. Five of the cultures revealed *Klebsiella pneumoniae*; two of them revealed *Pseudomonas aeruginosa* and one *Acinetobacter baumannii*. In one patient in the neonatal intensive care unit, *S. marcescens* was found positive in the cerebrospinal fluid and blood culture simultaneously.

Twenty-six (57.8%) isolates of *S. marcescens* produced extended-spectrum beta-lactamases (ESBL), and eighteen (40%) isolates produced carbapenemase. Isolates of two of the patients who died produced ESBL and carbapenemases. Nineteen (42.2%) of them were non-MDR, fourteen (31.1%) were MDR, eleven (24.4%) were XDR, one (2.2%) was PDR (Figure 1). *S. marcescens* isolates were examined in the fatal group; two had MDR, one had non-MDR, and one had XDR.

All patients received antimicrobial treatment: five (11.1%) patients were treated with monotherapy, 16 (35.5%) received a combination of two antibiotics, and 24 (53.4%) were treated with a regimen including ≥ 3 antibiotics. All XDR and three MDR isolates were treated with a high-dose prolonged infusion of meropenem. The most common regimens received for XDR isolates were a high-dose prolonged meropenem infusion, amikacin, levofloxacin, and tigecycline. Most of the patients with MDR isolates received meropenem, amikacin, and levofloxacin.

The medical staff's hands and environmental cultures were negative. The medical staff received training for nosocomial infections.

Table 1. Patient demographics, clinical characteristics and most common underlying diseases of the patients with *S. marcescens* bacteremia

Characteristics	Total cases (n= 45)	Fatal group	Non-fatal group
Age, month, median	37.6 (1-198)	80.75	33.35
Male, n (%)	24 (66.7)	3	21
Underlying disease, n (%)			
Hematological-oncological disorders	12 (26.9)	1	11
Neuromuscular disease	10 (22.2)		10
Prematurity	8 (17.7)		8
Cardiovascular diseases	6 (13.3)	2	4
Abdominal surgery	5 (11.1)		5
Liver transplantation	1 (2.2)		1
Immune deficiency	1 (2.2)	1	
Chronic lung disease	1 (2.2)		1
Metabolic syndrome	1 (2.2)		1
Service, n (%)			
PICU	28 (62.2)		
NICU	8 (17.7)		
Hematology-oncology	6 (13.3)		
Pediatric surgery	3 (6.6)		
Had CVC, n	43		
Clinical manifestation, n (%)			
BSI	24 (53.3)	3	21
CR-BSI	21 (46.7)	1	20
Bacteria resistance profile, n (%)			
Non-MDR	19 (42.2)	1	18
MDR	14 (31.1)	2	12
XDR	11 (24.4)	1	10
PDR	1 (2.2)	1	1
Polymicrobial, n (%)	8 (17.8s)	0	8
Laboratory data			
Leukocyte count/mm ³	13.87 (0.5-36.7)	17.20	13.54
C-reactive protein level mg/L	124.7 (1-395)	147.2	122.5
Serum albumin level (g/dL)	2.76 (1-4.1)	2.43	2.79
Catheter removal	24 (55.8)	3	21
Length of hospital stay, day (mean)	43.20 (3-171)	42.7	38.5
The duration of CVC prior to catheter related BSI, day (mean)	47.9 (1-200)	46.02	32.50
28-day outcome, n (%)	4 (8.9)		

PICU: Pediatric intensive care unit, NICU: Neonatal intensive care unit, CVC: Central venous catheter, BSI: Bloodstream infections, CR-BSI: Catheter-related bloodstream infections, MDR: Multidrug-resistant, XDR: Extensively drug-resistant, PDR: Pandrug-resistant.

Discussion

S. marcescens is a severe nosocomial infection cause. Furthermore, multidrug-resistant *S. marcescens* strains are known to increase (4,7,17,18).

Within twenty months, 45 BSI episodes were identified in our study, and blood cultures were positive for *S. marcescens*

with a high prevalence of ESBL and carbapenemase production. The all-cause 28-day mortality rate was 8.9%. Herein, it was aimed to examine patients' demographics, clinical characteristics, the most common underlying diseases, and treatment. In addition, the factors associated with *S. marcescens*-related mortality were aimed to be identified.

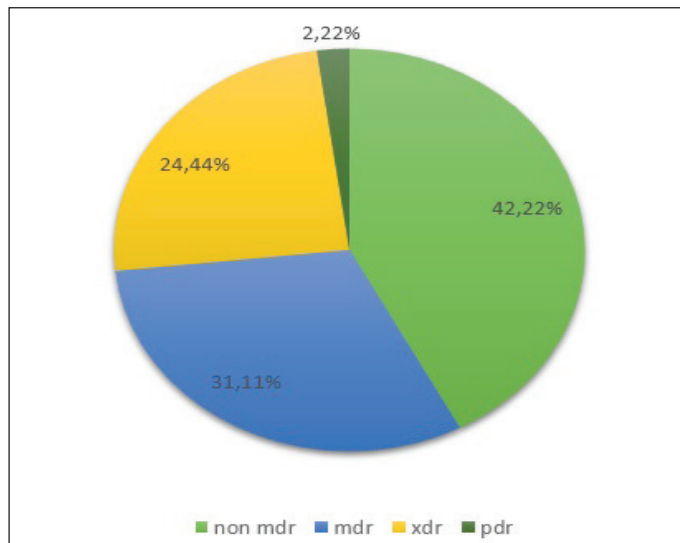


Figure 1. Resistance profile of *S. marcescens*.

Cheng et al. (19) have demonstrated a prevalence of 12% for ESBL production among *S. marcescens*. Bouchillon et al. (20) have reported that the percentage of carbapenem-resistant *S. marcescens* remained low worldwide, as less than or equal to 2%. However, in our study, 57.8% of the isolates of *S. marcescens* produced ESBL, and 40% of the isolates produced carbapenemase. Choi et al. (18) have reported that the most critical risk factor for resistant *Serratia* bacteremia was using a second or third-generation cephalosporin priorly. Our study patients were hospitalized in the intensive care unit, had underlying diseases, and used a broad spectrum of antimicrobial therapy; therefore, a high antibiotic resistance pattern was seen. *S. marcescens* isolates are naturally resistant to polymyxins, and those producing ESBL and carbapenemase severely constitute a concern. Therefore, therapeutic options available for treatment were limited.

Increased morbidity and mortality with multiple drug-resistant strains has led to the search for new treatment modalities. Previous studies have reported double carbapenem combination, prolonged antimicrobial categories, high-dose prolonged-infusion of carbapenem, or combined salvage therapies with colistin, amikacin, levofloxacin, and tigecycline for patients with multidrug-resistant *Enterobacteriaceae* isolates (21-25). The dose of meropenem in systemic infections other than meningitis is 20 mg/kg/dose, by infusion every eight hours for 30 minutes. Beta lactam antibiotics demonstrate a time-dependent effect on bacterial eradication. Therefore, after the concentration at which maximum killing is achieved, it is more effective to prolong the time remaining above this concentration rather than increasing the dose of beta lactam antibiotics. A prolonged infusion strategy has a greater likelihood of attaining pharmacokinetic/pharmacodynamic targets and

may offer clinical benefit in patients with severe infections or less susceptible pathogens (26). In our study, 24 (53.4%) patients were treated with a regimen including ≥ 3 antibiotics. All XDR (11 patients) and three MDR isolates were treated with high-dose prolonged-infusion of meropenem (meropenem was dosed at 30 mg/kg/dose intravenously every six hours, infused three hours). The most common regimens received for XDR isolates were prolonged high-dose meropenem infusion, amikacin, levofloxacin, and tigecycline in our patients. Most of the patients with MDR isolates received meropenem, amikacin, and levofloxacin.

Laboratory finding of the patients who died were also examined. Mean WBC and mean serum CRP levels were higher compared to the non-fatal group. Mean serum albumin level was lower than the fatal-group. Kim et al. (7) have reported similar results in their research and revealed that these findings are related to mortality. In addition, underlying diseases are seen as the other factor of mortality in most of our patients. Four patients died in this 28-day period, and one of them had standard risk B-cell ALL with neutropenic phase while one patient had SCID. The other two patients had congenital heart diseases and heart failure, and they were supported with extracorporeal membrane oxygenation. In contrast, one other patient who had high-risk B-cell ALL and catheter-related BSI with pan drug resistance isolates survived. The important factor in this patient was that he was not in the neutropenic phase, and his catheter was removed in the early stage of infection under triple antibiotic combined therapy (high-dose prolonged-infusion of meropenem, amikacin, levofloxacin).

Among the limitations of the study; clustering of *S. marcescens* reproductions within 20 months makes us think of a healthcare-associated outbreak, but we could not show the factor in the environmental samples or in the hands of the medical staff.

Conclusion

In our study, reasons for lower mortality rate could be related to high-dose prolonged carbapenem infusion, combined dual or triple antibiotic treatment, and early removal of CVCs. We want to emphasize the role of *S. marcescens* in bacteremia and highlight the importance of surveillance procedures and hospital staff education. All cultures obtained from the medical staff's hands and environment were negative. However, bacteremia with the same resistant strains was not observed after surveillance procedures.

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