Research Article *Pamukkale Medical Journal*
doi:https://dx.doi.org/10.31362/patd.1513010

Received: 09.07.2024
Accepted: 03.09.2024
Area of Expertise: Clinical Sciences

Title: Evaluation of Enterobacterales bloodstream infections in hematologic cancer patients.
Short title: Bloodstream infections in hematologic cancer patients.

Abstract

Purpose: In this study, we aimed to evaluate the clinical and laboratory findings of hospitalized patients with Enterobacterales bacteremia/sepsis, the risk factors for mortality, and the therapeutic options for treating bloodstream infections (BSIs) caused by Enterobacterales.

Materials and methods: Patients hospitalized in the Oncology Hospital between January 2021 and December 2022 whose Enterobacterales species were isolated in blood cultures were included in the study. Blood cultures were incubated in the Autobio BC120 device. Isolated microorganisms were named using a Vitek-2 (bioMerieux, France) automated system. Antibiotic susceptibility tests were performed in the Vitek-2 system (bioMerieux, France) and the disc diffusion method. In addition, the demographic and laboratory data of the patients were evaluated. A total of 103 patients were included in the study during the two years. Only the first isolates from each patient were included in the study.

Results: The distribution of Enterobacterales isolates grown in blood cultures, in order of frequency were *Escherichia coli* (n:74, 63.25%), *Klebsiella pneumoniae* ssp *pneumoniae* (n:27, 23.1%), *Klebsiella pneumoniae* ssp *ozaenae* (n:2, 1.71%), *Klebsiella oxytoca* (n:1, 0.85%), *Enterobacter cloaceae* complex (n:10, 6.84%), *Citrobacter freundii* (n:1), *Proteus mirabilis* (n:1), *Salmonella* spp (n:1). The median (min-max) white blood cell count was $1.51x10^3$cells/uL (0.01-19.87), C-reactive protein (CRP) was 112.3 mg/L (0.06-546.0), procalcitonin was 7.35 µg/L (0.05-61.21), time between blood culture collection and growing signal was 11.33 (3-58) hours and the blood culture result report was three (1-8) days. Acute Myeloid Leukemia 40 (39.2%), B-cell Acute Lymphoblastic leukemia 18 (17.6%), Multiple Myeloma 11 (10.8%), Diffuse Large B-cell Lymphoma 11 (10.8%) were the most common diseases seen in Enterobacterales isolated patients from blood cultures.

Conclusion: Each hospital should conduct its evaluation and examine the patient profile to make the correct empirical antibiotic selection. It is crucial to develop a suitable algorithm for this purpose.

Keywords: Enterobacterales, bloodstream infections, hematologic cancer patients.

Makale başlığı: Hematolojik kanser hastalarında Enterobacterales kan dolaşımı enfeksiyonlarının değerlendirilmesi.

Kısa başlık: Hematolojik kanser hastalarında kan dolaşımı enfeksiyonları.

Öz

Amaç: Bu çalışmada Enterobacterales bakteriyemisi/sepsisi nedeniyle hastaneye yatırılan hastaların klinik ve laboratuvar bulgularını, mortalite için risk faktörlerini ve Enterobacterales'in neden olduğu kan dolaşımı enfeksiyonlarının (KDE) tedavisine yönelik tedavi seçeneklerini değerlendirmeyi amaçladık.

Gereç ve yöntem: Çalışmaya Ocak 2021 ile Aralık 2022 tarihleri arasında Onkoloji Hastanesi'nde yatan ve kan kültürlerinde Enterobacterales türlerine rastlanan hastalar dahil edildi. Kan kültürleri Autobio BC120 cihazında inkübe edildi. İzole edilen mikroorganizmalar Vitek-2 (bioMerieux, Fransa) otomatize sistem kullanılarak adlandırıldı. Antibiyotik duyarlılık testleri hem Vitek-2 sistemi (bioMerieux, Fransa) hem de disk difüzyon yöntemiyle yapıldı. Ayrıca, hastaların demografik ve laboratuvar verileri değerlendirildi. İki yıllık dönemde toplam 103 hasta çalışmaya dahil edildi. Her hastadan sadece ilk izolatlar çalışmaya dahil edildi.

Bulgular: Kan kültürlerinde üreyen Enterobacterales izolatlarının dağılımı sıklık sırasına göre; *Escherichia coli* (%63.25, n:74), *Klebsiella pneumoniae* ssp *pneumoniae* (%23.1, n:27), *Klebsiella pneumoniae* ssp *ozaenae* (%1.71, n:2), *Klebsiella oxytoca* (%0.85, n:1), *Enterobacter cloaceae* kompleks (%6.84, n:10), *Citrobacter freundii* (n:1), *Proteus mirabilis* (n:1), *Salmonella* spp (n:1) şeklindeydi. Ortalama (minimum-maksimum) lökosit sayısı 1.51x103 hücre/uL (0.01-19.87), C-reaktif protein (CRP) 112.3 mg/L (0.06-546.0), prokalsitonin 7.35 µg/L (0.05-61.21), kan kültürünün alınmasıyla üreme sinyali arasında geçen süre 11,33 (3-58) saat ve kan kültürü sonuç raporu üç (1-8) gün olarak belirlendi. Kan kültürlerinden Enterobacterales izole edilen hastalarda; Akut Myeloid Lösemi 40 (%39.2), B-hücreli Akut Lenfoblastik Lösemi 18 (%17.6), Multiple Myelom 11 (%10.8), Diffüz Büyük B-hücreli Lenfoma 11 (%10.8) en sık görülen hastalıklardı.

Sonuç: Doğru ampirik antibiyotik seçimini yapabilmek için her hastane kendi değerlendirmesini yapmalı ve hasta profilini incelemelidir. Bu amaçla uygun bir algoritma geliştirmek son derece önemlidir.

Anahtar kelimeler: Enterobacterales, kan dolaşımı enfeksiyonları, hematolojik kanser hastaları.

Introduction

Hematological patients are prone to many infectious complications during their treatment, with bloodstream infections (BSIs) standing out as the most significant cause of mortality and morbidity in this patient group. In hematopoietic stem cell transplantation (HSCT) patients, more than 50% of deaths occur as a result of infections within the initial 100 days post-transplantation. Enterobacterales species are notably common culprits of BSIs in this population [1, 2].

The use of carbapenems in Enterobacterales infections has seen a considerable rise since the appearance of extended-spectrum beta-lactamases. There has been a noticeable increase in the prevalence of Carbapenem-Resistant Enterobacteriaceae (CRE) in the last few years. In 2017, the World Health Organization designated CRE as a pathogen of critical priority [3]. Due to plasmid-mediated horizontal gene transfer, CRE isolates have spread in hospitals, becoming a significant cause of death in immunosuppressive individuals. The most effective therapeutic approach for CRE bloodstream infections (BSIs) remains unknown. Therefore, this study aims to evaluate the clinical aspect and laboratory findings of hospitalized patients with Enterobacterales bacteremia/sepsis, identify risk factors for mortality, and propose possible treatment alternatives for the management of BSIs caused by Enterobacterales.

Material and method

Patients who were admitted to the hematology service and bone marrow transplant unit at Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital between January 2021 and December 2022 and had Enterobacterales species isolated in blood cultures were included. The hospital primarily serves hematologic and oncologic patients in Ankara, Türkiye. The study protocol received approval from the ethical committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital.

Blood culture samples taken from the patients were sent to the Medical Microbiology Laboratory. Subsequently, blood cultures were incubated in the Autobio BC120 (Autobio, Chinese) device and the blood culture bottles indicating growth were inoculated onto 5% sheep blood agar, eosin methylene blue agar, and chocolate agar media. Isolated microorganisms underwent evaluation and the Vitek-2 automated system (bioMerieux, France) was utilized for microbial typing. Antibiotic susceptibility was determined using both the Vitek-2 system and the disc diffusion method. Results of antibiotic susceptibility were interpreted following the guidelines of

the European Committee on Antimicrobial Susceptibility Testing (EUCAST), with those classified as S (Susceptible) and I (Intermediate) included in the sensitive group [4].

Furthermore, demographic data including age and gender, comorbid diseases, type of hematological malignancy, length of stay, empirical antibiotic use, antibiotics administered in post-culture treatment, concurrent infections, C-reactive protein (CRP) and procalcitonin levels, white blood cell counts and the duration times between blood culture collection and the growth signal of samples, were collected. The times and the laboratory's blood culture reporting data were also documented. The patients' immunosuppressive treatment options, bone marrow transplantation (BMT) status, type of transplantation, and neutropenia status were examined. Neutropenia was clinically categorized as mild when the absolute neutrophil count (ANC) ranged from 1000 to 1500/μL, moderate with an ANC between 500 and 1000/μL, or severe with an ANC below 500/μL. [5].

The data underwent analysis using SPSS (version 26) and were expressed as numbers, percentages, medians, minimum, and maximum values. Kaplan–Meier survival analysis was conducted to determine the 1-month survival rate.

Results

During the two-year study period, a total of 103 patients were included and 117 blood culture growths were detected. The study included the first samples from patients with recurrent growth. The average age of the patients was 47.5 years, with 45 patients being male (43.7%) and 58 females (56.3%).

In the study, Gram-negative microorganisms were isolated from 44.6% of the blood culture isolates, and among the Gram-negative, the rate of Enterobacterales was 70.9%. The distribution of Enterobacterales isolates in blood cultures, in order of frequency, were as follows: Escherichia coli (n:74, 63.25%), *Klebsiella pneumoniae* ssp *pneumoniae* (n:27, 23.1%), *Klebsiella pneumoniae* ssp *ozaenae* (n:2, 1.71%), *Klebsiella oxytoca* (n:1, 0.85%), *Enterobacter cloaceae* complex (n:10, 6.84%), *Citrobacter freundii* (n:1), *Proteus mirabilis* (n:1), *Salmonella* spp (n:1) (Table 1). Additionally, non-Enterobacterales microorganisms were simultaneously isolated from blood cultures in nine patients [*Staphylococcus epidermidis* (n:4), *Staphylococcus hominis* (n:4), *Kocuria varians* (n:1)].

The antibiotic susceptibility rates of the Enterobacterales isolates were as follows ampicillin 8.6%, piperacillin/tazobactam 60.3%, gentamicin 65.5%, amikacin

92.1%, cefuroxime axetil 33%, ceftriaxone 42.1%, ceftazidime 42.5%, cefepime 52.7%, ciprofloxacin 23.4%, trimethoprim/sulfamethoxazole 13.8%, ertapenem 79.3%, imipenem 83.3%, meropenem 81.4%, ceftazidime/avibactam 91.8%. (Table 2). Antibiotic susceptibility percentages according to microorganism species are given in Table 3. Although colistin and tigecycline sensitivity has been studied with the device, it is not presented because it was not tested using the reference method recommended by EUCAST.

Demographic data, clinical characteristics, and laboratory findings of the patients are presented in Table 4. The median (min-max) white blood cell count was $1.51x10^3$ cells/uL (0.01-19.87), CRP 112.3 mg/L (0.06-546.0), procalcitonin 7.35 µg/L (0.05-61.21), with a time (hours) between blood culture collection and the growing signal recorded as 11.33 (3-58) hours. The blood culture result report took three (1-8) days. Comorbid disorders included diabetes in eight (8%), hypertension in 12 (12.1%), perianal abscess in 16 (16.8%) and other diseases (epilepsy, chronic kidney disease, rectum, thyroid diseases) in 17.5%. Regarding cancers, Acute Myeloid Leukemia accounted for 40 (39.2%), B-cell Acute Lymphoblastic Leukemia (B-ALL) for 18 (17.6%), Multiple Myeloma for 11 (10.8%) and Diffuse Large B-cell Lymphoma for 11 (10.8%) of the cases with Enterobacterales isolated from blood cultures. Hematopoietic stem cell transplantation (HSCT) was applied for 51 (50.5%) patients, with 36 (35.6%) receiving allogeneic and 15 (14.9%) receiving autologous HSCT. Immunosuppressive therapy with cyclosporine was administered to 28 patients (28.3%) and Graft Versus Host Disease occurred in one patient (0.97%).

One hundred (97%) patients were administered empirical antibiotic treatment, utilizing cefoperazone-sulbactam, piperacillin-tazobactam, meropenem, ertapenem, fosfomycin, colistin, vancomycin, teicoplanin, and linezolid either as monotherapy or in combination. For 72 (72%) patients, the antibiotic therapy was modified following the report of blood culture growth. Among them, 67 (67%) underwent escalation, while de-escalation was implemented for four (4%) patients. Antibiotic therapy choices remained unchanged for 29 (29%) patients. The overall 30-day mortality rate was 14.56% (Table 4).

Discussion

In recent years, antimicrobial resistance has become a significant problem due to the common use of broad-spectrum antibiotics, particularly among gram-negative bacteria. These bacteria are the major causes of bloodstream infections in

hospitalized patients, especially in hematology clinics. Therefore, it is crucial to enhance awareness of antimicrobial resistance by employing effective methods in education, training, and communication. It is necessary to ensure effective infection control and reduce the incidence of infection. It is important to increase economic opportunities to develop new antimicrobial drugs, vaccines, and diagnostic tools and ensure sustainability. A 2021 study conducted in Türkiye reported *K. pneumoniae* as the most prevalent cause of BSIs, followed by *S. aureus*. The reported rates of isolated microorganisms in the Turkish study were as follows: *K. pneumoniae* 18.42%, *S. aureus* 14.47%, *Acinetobacter* spp. 13.16%, *Escherichia coli* 13.16%, *Enterococcus faecalis* 11.39%, *Pseudomonas aeruginosa* 10.53%, *Candida* spp. 7.89% [6]. In a 2019 Italian study, *P. aeruginosa*, *E. coli*, *A. baumannii*, methicillin-resistant *S. aureus* and *K. pneumoniae* were identified as the most common causes of sepsis [7]. Various studies consistently report *E. coli*, *K. pneumoniae*, *Acinetobacter* spp., *Pseudomonas* spp. and *Enterobacter* spp. as the most frequently detected gram-negative agents in bacteremia and sepsis. According to a 2023 study conducted in our country, the frequency of causative gram-negative agents was 33.9% for *E. coli*, 19.1% for *K. pneumoniae*, 18.5% for *Acinetobacter* spp., 10.3% for *Pseudomonas* spp., and 4.6% for *Enterobacter* spp. [8]. In our study, 44.6% of blood culture isolates were identified as gram-negative microorganisms, with Enterobacterales constituting 70.9% among gram-negatives. The distribution of Enterobacterales isolates in blood cultures, in order of frequency, were *E. coli* (63.25%), *K*. *pneumoniae* ssp *pneumoniae* (23.1%), *K. pneumoniae* ssp *ozaenae* (1.71%), *Klebsiella oxytoca* (0.85%), *Enterobacter cloacae* complex (6.84%), *Citrobacter freundii* (0.85%), *Proteus mirabilis* (0.85%), *Salmonella* spp (0.85%). We emphasize the importance for each hospital to identify the most common causes of sepsis, as the distribution of microorganisms may vary among hospitals and countries.

Nowadays, multidrug resistant microorganisms are the major public health problem. Gram-negative bacteria are the major causes of bloodstream infections in patients hospitalized. A 2023 study in Türkiye revealed antibiotic resistance rates of Enterobacterales isolates ranging from 6.8% to 14.5% for carbapenems, 10.6% for amikacin, 70.3% for ampicillin, 63.6% for cefuroxime, 55.4% for ceftriaxone, 48.9% for cefepime, 44.1% for trimethoprim/sulfamethoxazole (SXT), 53.8% for ciprofloxacin and 27.5% for piperacillin-tazobactam [8]. In our study, the resistance rates (%) of Enterobacterales isolates were as follows: ampicillin 91.4%, cefuroxime 67.9%,

ceftriaxone 57.9%, cefepime 51.7%, SXT 86.3%, ciprofloxacin 71.2%, piperacillin-tazobactam 40.2%. Additionally, resistance rates for ceftazidime-avibactam was found to be 8.2%. Meropenem resistance rates were 4% in *E. coli* and 45.4% in *K. pneumoniae* isolates. Ceftazidime/avibactam resistance rates were 2.2% in *E. coli*, 23.3% in *K. pneumoniae* and 42.9% in *Enterobacter cloacae* complex. Our study revealed that 97% of patients, with gram-negative bacteremia/sepsis developed under extended-spectrum empirical antibiotic treatment, with escalation applied for 67% of the patients. The study underscored the emergence of antibiotic resistance in Enterobacterales isolates, particularly in carbapenem-resistant *K. pneumoniae* (CRKP), as a pressing issue in our hospital. In response, hospitals should implement stringent infection control measures, including hand hygiene for hospital staff, training initiatives, patient isolation, and comprehensive disinfection sterilization practices.

Multidrug-resistant Enterobacterales BSIs have been related to a poor prognosis, with reported all-cause mortality rates ranging from 32.9% to 70% in severe CRE BSIs. A 2021 study by Zhou C, involving 208 CRE patients, found an overall 30-day mortality rate of 46.2%, with 85.6% of deaths attributed to CRKP isolated from blood cultures [3]. The study identified a short duration of antimicrobial therapy and empirical use of tigecycline as independent risk factors for mortality. Tigecycline treatment showed poor therapeutic effects on BSIs patients, whereas carbapenem treatment demonstrated better efficacy, especially in patients infected by meropenem minimum inhibitory concentration (MIC)≤8 mg/L isolates. Additionally, a shorter duration of antimicrobial therapy was associated with a poorer prognosis compared to longer-duration therapy [3]. In our study, the 30-day mortality rate was 14.56%, and this rate was higher for K. pneumoniae BSIs, emphasizing the clinical relevance of the findings in the context of Enterobacterales infections.

On the other hands, various factors, including individual risk factors, comorbid diseases, immunosuppression and the presence of cancer can significantly influence the prognosis of infection. Central venous catheters and urinary catheters, may contribute to mucosal damage, thereby increasing the incidence of BSIs [9]. A large-scale study by Sava et al. [10] showed that; BSI is a prevalent infectious complication after allogeneic HSCT, occurring in 20-60% of HSCT patients in the pre- and post-engraftment phases, as well as in patients with acute graft-versus-host disease. In the same study involving 1432 HSCT patients, acute leukemia was the most common underlying condition (53.2%), with 95.2% of patients undergoing a single allogeneic transplantation. The study reported that over a median follow-up time of 1.88 years,

33.1% of patients experienced at least one BSI. The highest incidence of BSI was observed in the peri-transplantation phase of the second transplant (30.6%). Many studies have indicated high BSI rates, particularly within the first 30 days after HSCT, even in cases where quinolone prophylaxis was used [11-13]. In our study involving patients with hematological diseases, Acute Myeloid Leukemia (39.2%), B-ALL leukemia (17.6%), Multiple Myeloma (10.8%) and Diffuse Large B-cell Lymphoma (10.8%) were the most common hematologic cancers in BSI patients. Of the patients, 28.3% received cyclosporine and bone marrow transplantation was performed in 50.5% of the patients, with 35.6% receiving allogeneic and 14.9% receiving autologous bone marrow transplantation. We recommend further BSI studies with a high number of HSCT patients, specifically evaluating the timing of BSI occurrence.

Blood culture is frequently the primary diagnostic method for identifying BSIs. Blood samples should be collected before administering medication, but the culture process is time-consuming, leading to delays in obtaining results [14]. In a 2023 study in Barcelona, the association between mortality and delays in reporting blood culture positivity in 6225 patients with bacteremia treated at a Barcelona hospital were evaluated, retrospectively. The study found that reporting delays for Enterobacterales increased the risk of death, and 77.8% of patients who died from an Enterobacterales BSI experienced delayed reporting [15]. In our study, the average time between blood culture collection and the growth signal was 11.33 hours, and the average blood culture result reporting time after signaling bacterial growth was three days. These results emphasize the need for an effective antimicrobial stewardship program and rapid molecular-based diagnostic methods to facilitate the early detection of causative agents in BSIs in our hospital.

In the early diagnosis of infectious diseases, various parameters are commonly utilized, with CRP being the most frequently employed among them. While some studies indicate that CRP's diagnostic value in sepsis is moderate and its predictive value for positive blood culture and disease prognosis is lower compared to procalcitonin, CRP levels generally show a decline within the first 48 hours following the initiation of infection treatment. Procalcitonin's advantage as a biomarker for predicting infection lies in its high in vitro stability and serum levels can elevate within a span of 2 to 3 hours following the onset of infection. Although procalcitonin's specificity for infection is not absolute, when the serum procalcitonin content exceeds 2.0 ng/ml, the risk of sepsis or septic shock increases significantly [16]. In our study, increased CRP and procalcitonin levels were observed in most

patients [CRP in 101 patients (normal range: 0-5 mg/L), Procalcitonin in 97 patients (normal range: 0-0.1 µg/L)], with average CRP and procalcitonin levels of 112.3 mg/L and 7.35 µg/L, respectively. Our findings suggest that CRP and procalcitonin can serve as additional diagnostic tests for BSIs.

In conclusion, our study focused on patients with hematological cancer, revealing that *E. coli* and *K. pneumoniae* were the most commonly isolated microorganisms in BSIs among Enterobacterales. The resistance rates to meropenem were 4% in *E. coli* and 45.4% in *K. pneumoniae* isolates, while ceftazidime/avibactam resistance rates were 2.2% in *E. coli* and 23.3% in *K. pneumoniae*. Notably, 97% of patients developed gram-negative bacteremia/sepsis under extended-spectrum empirical antibiotic treatment, with a 30-day mortality rate of 14.56%, which was higher for *K. pneumoniae*-associated BSIs. Hematologic cancers such as Acute Myeloid Leukemia and B-ALL were predominant among BSI patients. Cyclosporine was administered to 28.3% of the patients, and BSIs were common in BMT patients, with 35.6% receiving allogeneic and 14.9% receiving autologous BMT. Our study highlighted an average blood culture result reporting time of three days after signaling bacterial growth. Elevated levels of CRP and procalcitonin were observed in most patients, suggesting their potential as additional diagnostic tests for BSIs. The study emphasized the importance of an effective antimicrobial stewardship program and rapid molecular-based diagnostic methods for early detection of causative agents in BSIs within our hospital. Furthermore, the study underscored the emerging challenge of antibiotic resistance in Enterobacterales isolates, particularly in CRKP. As a response, strict infection control measures, including hand hygiene for hospital staff, training, patient isolation and comprehensive disinfection-sterilization practices, were recommended. Finally, the study proposed further research on BSIs, particularly focusing on a larger cohort of HSCT patients to evaluate the timeline of BSIs. Each hospital should conduct its own evaluation and examine the patient profile to make the correct empirical antibiotic selection. It is crucial to develop a suitable algorithm for this purpose.

There were some study limitations. EUCAST recommends the broth microdilution method for colistin antibiotic susceptibility testing. However, since the broth microdilution kit was not available in our laboratory, Vitek was used instead. Although colistin and tigecycline sensitivity has been studied with the device, it is not presented because it was not tested using the reference method recommended by EUCAST.

Conflict of interest: No conflict of interest was declared by the authors.

References

1. Santos ES, Lima ACM, Breda GL, et al. Colonization by multidrug-resistant bacteria in hematological patients undergoing hematopoietic stem cell transplantation and clinical outcomes: a single-center retrospective cohort study. Transpl Infect Dis 2023;25:e14119. https://doi.org/10.1111/tid.14119
2. Huang QS, Han TX, Fu HX, et al. Prognostic factors and outcomes in patients with septic shock after allogeneic hematopoietic stem cell transplantation. Transplant Cell Ther 2024;30:310(e1-11). https://doi.org/10.1016/j.jtct.2023.12.013
3. Zhou C, Jin L, Wang Q, et al. Bloodstream infections caused by carbapenem-resistant Enterobacterales: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. Infect Drug Resist 2021;14:731-742. https://doi.org/10.2147/IDR.S294282
4. The European Committee on Antimicrobial Susceptibility Testing-EUCAST Guidelines for Clinical Break Point. Clinical Breakpoints-Bacteria (v 11.0), 2021 and (v 12.0), 2022. Available at: https://www.eucast.org/clinical_breakpoints. Accessed March 01, 2024
5. Boxer LA. How to approach neutropenia. Hematology Am Soc Hematol Educ Program 2012;2012:174-182. https://doi.org/10.1182/asheducation-2012.1.174
6. Hökenek UD, Özcan FG, Sevdi MS, Erkalp K, Selcan A. Mortality predictors in sepsis: a retrospective study. J Turk Soc Intens Care 2021;19:82-89. https://doi.org/10.4274/tybd.galenos.2020.30074
7. Busani S, Serafini G, Mantovani E, et al. Mortality in patients with septic shock by multidrug resistant bacteria: risk factors and impact of sepsis treatments. J Intensive Care Med 2019;34:48-54. https://doi.org/10.1177/0885066616688165
8. Kalaycı ÇZ, Behçet M, Avcıoğlu F, Afşar Y, Şentürk E, Kurtoğlu M. Kan kültürü örneklerinden izole edilen gram negatif bakterilerin antibiyotik direnç profillerinin incelenmesi. Value in Health Sciences 2023;13:80-86. https://doi.org/10.33631/sabd.1133713
9. Li Y, Li J, Hu T, et al. Five-year change of prevalence and risk factors for infection and mortality of CRKP bloodstream infection in a tertiary hospital in North China. Antimicrob Resist Infect Control 2020;9:79. https://doi.org/10.1186/s13756-020-00728-3

10. Sava M, Bättig V, Gerull S, et al. Bloodstream infections in allogeneic haematopoietic cell recipients from the Swiss Transplant Cohort Study: trends of causative pathogens and resistance rates. Bone Marrow Transplant 2023;58:115-118. https://doi.org/10.1038/s41409-022-01851-y
11. Carreira AS, Salas MQ, Remberger M, et al. Bloodstream infections and outcomes following allogeneic hematopoietic cell transplantation: a single-center study. Transplant Cell Ther 2022;28:50(e1-8). https://doi.org/10.1016/j.jtct.2021.10.008
12. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. Transpl Infect Dis 2014;16:106-114. https://doi.org/10.1111/tid.12175
13. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 2009;15:47-53. https://doi.org/10.1016/j.bbmt.2008.10.024
14. Senok A, Dabal LA, Alfaresi M, et al. Clinical impact of the Biofire Blood Culture Identification 2 Panel in adult patients with bloodstream infection: a multicentre observational study in the United Arab Emirates. Diagnostics (Basel) 2023;13:2433. https://doi.org/10.3390/diagnostics13142433
15. Fidalgo B, Morata L, Cardozo C, et al. Information delay of significant bloodstream isolates and patient mortality: a retrospective analysis of 6225 adult patients with bloodstream infections. Clin Infect Dis 2023;77:680-686. https://doi.org/10.1093/cid/ciad243
16. Zhang Y, La M, Sun J, et al. Diagnostic value and prognostic significance of procalcitonin combined with C-reactive protein in patients with bacterial bloodstream infection. Comput Math Methods Med 2022;2022:6989229. https://doi.org/10.1155/2022/6989229

Ethics committee approval: Permission for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital (11.01.2024, Research Code No: 2023-12/126).

Authors' contributions to the article

T.D., E.T constructed the main idea and hypothesis of the study. E.T., F.A. collected data. T.D., S.S.Y., T.U. developed the theory and arranged the material and method section. E.T., T.D. have done the evaluation of the data in the results section. Discussion section of the article written by T.D and E.T. Also I.M., A.S.G., N.I. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Table 1. Distribution of Enterobacterales isolates grown in blood cultures

Isolated microorganism	**Number (n=117)**	**Percent (%)**
Escherichia coli	74	63.25
Klebsiella pneumoniae* ssp *pneumoniae	27	23.1
***Enterobacter cloacae* complex**	8	6.84
***Enterobacter* spp.**	2	1.71
Klebsiella pneumoniae* ssp *ozaenae	2	1.71
Citrobacter freundii	1	0.85
Klebsiella oxytoca	1	0.85
Proteus mirabilis	1	0.85
***Salmonella* group**	1	0.85
Total	117	100.0

Table 2. Antibiotic susceptibility rates of the blood culture Enterobacterales isolates

Antibiotic	Resistance, n (%)	Susceptible, n (%)	Total
Amikacin	9 (7.9)	105 (92.1)	114
Ampicillin	96 (91.4)	9 (8.6)	105
Cefazolin	75 (97.4)	2 (2.6)	77
Cefepime	53 (47.3)	59 (52.7)	112
Cefoperazone/Sulbactam	27 (23.3)	89 (76.7)	116
Cefotaxime	12 (63.2)	7 (36.8)	19
Ceftazidime	65 (57.5)	48 (42.5)	113
Ceftazidime/Avibactam	6 (8.2)	67 (91.8)	73
Ceftriaxone	66 (57.9)	48 (42.1)	114
Cefuroxime axetil	75 (67.0)	37 (33.0)	112
Ciprofloxacin	85 (76.6)	26 (23.4)	111
Ertapenem	24 (20.7)	92 (79.3)	116
Gentamicin	38 (34.5)	72 (65.5)	110
Imipenem	18 (16.7)	90 (83.3)	108
Meropenem	22 (18.6)	96 (81.4)	118
Piperacillin/Tazobactam	46 (39.7)	70 (60.3)	116
Trimethoprim/Sulfomethoxazole	100 (86.2)	16 (13.8)	116

Table 3. Antibiotic susceptibility of isolated strains in blood culture

Antibiotics	***Escherichia coli*** **(%)**	***Klebsiella pneumoniae*** **ssp *pneumoniae*** **(%)**	***Enterobacter cloacae*** **complex (%)**	***Entero bacter*** **spp. (%)**	***Klebsiella pneumoniae*** **ssp *ozaenae*** **(%)**	***Citrobacter freundii*** **(%)**	***Klebsiella oxytoca*** **(%)**	***Proteus mirabilis*** **(%)**	***Salmonella*** **group (%)**
Amikacin	71/71 (100)	20/27 (74.1)	8/8 (100)	1/2 (50)	1/2 (50)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Ampicillin	7/71 (9.9)	0/26 (0)	0/0 (0)	0/2 (0)	0/2 (0)	0/0(0)	0/1 (0)	0/1 (0)	1/1 (100)
Cefazolin	2/41 (4.9)	0/24 (0)	0/7 (0)	0/0 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/0 (0)
Cefepime	43/70 (61.4)	4/27 (14.8)	3/8 (37.5)	0/2 (0)	0/1 (0)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Cefoperazone/ Sulbactam	68/74 (90.7)	13/26 (50)	3/8 (37.5)	1/2 (50)	1/2 (50)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Ceftazidime	39/71 (54.9)	3/27 (11.1)	3/8 (37.5)	0/2 (0)	0/1 (0)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Ceftazidime/ Avibactam	45/46 (97.8)	13/15 (86.7)	4/7 (57.1)	1/1 (100)	2/2 (100)	1/1 (100)	-	-	1/1 (100)
Ceftriaxone	41/73 (56.2)	3/27 (11.1)	1/8 (12.5)	0/1 (0)	0/1 (0)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Cefuroxime axetil	30/72 (41.7)	2/26 (7.7)	1/8 (12.5)	-	1/2 (50)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Ciprofloxacin	19/69 (27.5)	3/27 (11.1)	2/7 (28.6)	1/2 (50)	1/2 (50)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Ertapenem	70/74 (94.6)	14/27 (51.9)	3/8 (37.5)	1/2 (50)	1/1 (100)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Gentamicin	51/70 (72.9)	13/25 (52)	5/7 (71.4)	0/2 (0)	1/2 (50)	0/1 (0)	1/1 (100)	0/1 (0)	1/1 (100)
Imipenem	69/71 (97.2)	14/27 (51.9)	3/4 (75)	1/2 (50)	1/1 (100)	1/1 (100)	0/1 (0)	0/0 (0)	1/1 (100)
Meropenem	72/75 (96)	15/27 (55.6)	3/8 (37.5)	1/2 (50)	2/2 (100)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Piperacillin/ Tazobactam	56/74 (75.7)	8/27 (29.6)	3/8 (37.5)	0/2 (0)	0/1 (0)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
Trimethoprim/ Sulfomethoxazole	7/74 (9.5)	6/27 (22.2)	1/8 (12.5)	1/2 (50)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	1/1 (100)

Table 4. Demographic, clinic and laboratory characteristics of the patients

Variables	Median (min-max)
Age, years	47.50 (20-77)
Laboratory findings during blood culture growth	
White blood cell (x10^3cells/uL)	1.51 (0.01-19.87)
CRP (mg/L)	112.3 (0.06-546.0)
Procalcitonin (µg/L)	7.35 (0.05-61.21)
Time between blood culture collection and growing signal (hours)	11.33 (3-58)
Blood culture result report (days)	3 (1-8)
	N (%)
Gender	
Female (n, %)	58 (56.3)
Male (n, %)	45 (47.7)
Comorbid Diseases (n, %)	
Diabetes	8 (8)
Hypertension	12 (12.1)
Perianal Abscess	16 (16.8)
Other diseases (epilepsy, chronic kidney disease, rectum, thyroid diseases)	18 (17.5)
Hematological diagnoses (n, %)	
Multiple Myeloma	11 (10.8)
Acute Myeloid Leukemia	40 (39.2)
B cell- Acute Lympholastic leukemia	18 (17.6)
T cell- Acute Lympholastic leukemia	4 (3.9)
Diffuse large B-cell lymphoma	11 (10.8)
Chronic Lymphocytic leukemia	2 (2.0)
Aplastic anemia	3 (2.9)
Marginal Zone Lymphoma	1 (1.0)
Burkitt Lymphoma	1 (1.0)
Hodgkin Lymphoma	5 (4.9)
NK/T cell Lymphoma	2 (2.0)
Mantle cell lymphoma	2 (2.0)
Thrombotic Thrombocytopenic Purpura	1 (1.0)
Graft Versus Host Disease (GVHD) (n, %)	1 (0.97)
Bone Marrow Transplantation (BMT) (n, %)	51 (50.5)
Allogeneic	36 (35.6)
Autologous	15 (14.9)
Patients receiving empirical antibiotic treatment (n, %)	100 (97)
Patients whose antibiotic therapy was changed after report of blood culture growth (n, %)	72 (72)
İmmunosuppressive therapy use (n, %)	
Cyclosporine	28 (28.3)

Antimicrobials used in empirical treatment	Cefoperazone/sulbactam Piperacillin/tazobactam Piperacillin/tazobactam + Vancomycin Cefoperazone/sulbactam + Vancomycin Cefoperazone/sulbactam + Teicoplanin Meropenem Meropenem + Teicoplanin Meropenem + Vancomycin Ertapenem Linezolid Fosfomycin + Colistin
Antimicrobials used in post-culture treatment	Cefoperazone/sulbactam Piperacillin/tazobactam Piperacillin/tazobactam + Vancomycin Cefoperazone/sulbactam + Vancomycin Cefoperazone/sulbactam + Teicoplanin Cefoperazone/sulbactam + Linezolid Imipenem Imipenem + Colistin Meropenem Meropenem + Teicoplanin Meropenem + Vancomycin Ertapenem Fosfomycin + Colistin Meropenem + Colistin + Vancomycin Meropenem + Colistin + Daptomycin Meropenem + Vancomycin + Metronidazole Meropenem+ Linezolid + Fosfomycin Meropenem + Tigecycline + Colistin Colistin + Fosfomycin Colistin + Fosfomycin + Meropenem Ceftazidime + Fosfomycin + Linezolid
Post culture antimicrobial therapy (n, %)	
Escalation	67 (67%)
Deescalation	4 (4%)
No change	29 (29%)
30 day-mortality (n, %)	15 (14.56%)

Tavukcu E, Arslan F, Suzuk Yildiz S, Gureser AS, Mumcuoglu I, Inan N, Ulas T. Evaluation of Enterobacterales bloodstream infections in hematologic cancer patients. Pam Med J 2025;18:…-…

Tavukcu E, Arslan F, Süzük Yıldız S, Güreser AS, Mumcuoğlu İ, İnan N, Ulaş T. Hematolojik kanser hastalarında Enterobacterales kan dolaşımı enfeksiyonlarının değerlendirilmesi. Pam Tıp Derg 2025;18:…-…

Esra Tavukcu, Asist. Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: md.esratavukcu@gmail.com (https://orcid.org/0009-0005-6638-7492) (Corresponding Author)

Ferzan Arslan, Asist. Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: md.ferzanarslan@gmail.com (https://orcid.org/0000-0002-7623-1855)

Serap Süzük Yıldız, Assoc. Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: serapsuzuk@gmail.com (https://orcid.org/0000-0002-4820-6986)

Ayşe Semra Güreser, Assoc. Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: semrakalay@yahoo.com (https://orcid.org/0000-0002-6455-5932)

İpek Mumcuoğlu, Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: ipekmumcuoglu@gmail.com (https://orcid.org/0000-0002-6392-8880)

Neşe İnan, M.D. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: neseurdogan@yahoo.com (https://orcid.org/0000-0002-1559-6244)

Turgay Ulaş, Prof. Department of Hematology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: turgayulas@yahoo.com (https://orcid.org/0000-0001-9332-663X)

Tuba Dal, Prof. Department of Medical Microbiology, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye, e-mail: tuba_dal@yahoo.com (https://orcid.org/0000-0001-7045-1462)