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Original Article

Antibiotic resistance patterns of multidrug resistant bacteria in acute myeloid leukemia patients during induction treatment

Lazar Trajković[1], Mirjana Cvetković[1], Mirjana Mitrović[1,2], Zlatko Pravdić[1,2], Nikola Pantić[1], Nikica Sabljić[1], Ljubomir Jaković[1], Ana Vidović[1,2], Nada Suvajdžić-Vuković[1,2], Marijana Virijević[1,2]

[1] *Clinic of Hematology, University Clinical Centre of Serbia, Belgrade, Serbia*
[2] *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*

Abstract
Introduction: The treatment of acute myeloid leukemia (AML) is accompanied by infectious complications, particularly during induction. The surge of multi-drug resistant (MDR) bacteria represents an additional problem for the health care of patients with AML.
Methodology: A retrospective analysis of infectious complications was performed in 84 patients with AML undergoing induction therapy hospitalized between October 2020 and April 2023 at the Clinic of Hematology, University Clinical Centre of Serbia.
Results: From 84 patients and 95 bacterial isolates, *Enterococcus* spp. was the most frequent Gram-positive bacterium (26%), showing a 56% resistance rate to vancomycin, and a 77.3% resistance rate to carbapenems, with a 4.3% resistance rate to linezolid and no resistance to tigecycline detected. The most common Gram-negative bacterium, *Klebsiella* spp. (28%), was resistant to cephalosporins, carbapenems, fluoroquinolones (88%, 84.6%, and 88.5% respectively), with a sizeable resistance rate to ceftazidime/avibactam and colistin (20% and 36.4% respectively). XDR *Klebsiella* spp. dominated the isolated strains, being detected in 57.7% of cultures, whereas *Enterococcus* spp. was identified as MDR or XDR in 40% and 28% respectively. The factors associated with developing MDR infections were ECOG PS > 2 (p = 0.024), sepsis (p = 0.0016), and the presence of two or more infectious syndromes (p = 0.016). Patients with a confirmed MDR bacterial infection had a mortality rate of 36.7%.
Conclusions: Our work demonstrates that the frequency of infections in this population is high, especially with MDR and XDR strains of *Klebsiella* spp. and *Enterococcus* spp., which are accompanied by high rates of early death.

Key words: MDR; AML; antibiotic resistance; induction.

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Introduction

The treatment of acute myeloid leukemia (AML) is often accompanied by infectious complications, particularly during induction. These complications are frequently caused by microorganisms with a high antimicrobial resistance rate, associated with a high mortality rate in these patients [1]. Patients with acute leukemia are at increased risk of developing infections both as a result of the leukemia and its treatment. Neutropenia is the primary risk factor associated with the development of infection [2]. Additionally, the incidence of therapy-related mortality rises with age, associated comorbidities, and poor performance status [3]. In 42-72% of patients with AML, infections are present at the time of diagnosis [4,5].

In recent years, an increase in febrile neutropenia caused by Gram-positive bacteria in comparison to Gram-negative bacteria has been reported [6,7]. However, some publications still point to the predominance of Gram-negative bacteria during AML induction [4,5]. Nonetheless, despite improved diagnostic capabilities the identification of causative infectious agents in febrile neutropenia is possible in only 20-50% of cases [7–9]. Despite improved measures of supportive therapy, the mortality of patients with febrile neutropenia and microbiologically confirmed septicemia reaches 15-25%, especially in developing countries [10–12].

The surge of multi-drug resistant (MDR) bacteria [13] represents an additional problem and burden for the health care of patients with AML. The bacteria known as ESCAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp.)* are considered to have the highest impact on patient mortality on a global scale [14].

During the COVID-19 pandemic patients with hematological malignancies, especially AML, were increasingly vulnerable to COVID-19 infection and associated concomitant or subsequent secondary infections showing a great impact on outcomes [15,16].

This paper aims to retrospectively analyze and create an overview of the most common causes of bacterial infectious complications in AML patients receiving intensive chemotherapy, the prevalence of MDR bacteria, their antibiotic resistance patterns, and associated risk factors for acquiring MDR bacterial infections and early death (ED).

Methodology

This retrospective analysis was performed at the Clinic for Hematology, University Clinical Center of Serbia (UCCS) in the period from October 2020 to April 2023. The study included 84 patients diagnosed with AML according to the diagnostic criteria of the World Health Organization 2016 [17]. Risk stratification and treatment were done according to the European LeukemiaNet (ELN) 2017 recommendations on the management of AML [18]. Patients were treated in single or two-bedrooms with "high-efficiency particulate air" (HEPA) filters. A central venous line (CVL) was placed in all patients. All patients were screened at admission (throat, nasal, axillary, inguinal, and rectal swab, urine culture, HIV, infectious hepatitis serology). All patients received antimicrobial prophylaxis as per local policy (fluoroquinolones, 67 (79.7%) received itraconazole, while 17 (20.3%) received fluconazole) [18]. Blood samples for culture were obtained at each workup of a febrile episode (FE) during hospitalization. In addition, according to clinical indications, other samples (urine, wound swabs, stool, etc.) were taken for microbiological analysis. After a bacterium was identified, the antibiotic sensitivity or resistance was assessed using Vitek 2 compact (Biomerieux, France) in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for designating an organism as susceptible (S), susceptible, increased exposure (I), and resistant (R).

Table 1. Baseline characteristics of the patients.

Baseline characteristics	Value
Age-median (years), range	56 (18-71)
EMD- lymphadenopathy (%)	10 (11.9%)
EMD- hepatosplenomegaly (%)	17 (20.2%)
ECOG PS > 2	
Yes (N, %)	8 (9.6%)
No (N, %)	75 (90.4%)
HCT-CI ≥ 3	
Yes (N, %)	15 (17.9%)
No (N, %)	69 (82.1%)
BMI kg/m^2, mean, SD	27.3 ± 6.5
WBC – median (× 10^9/L), range	4.1 (0.3-210)
WBC > 30 × 10^9/L, N (%)	25 (29.8%)
Hb – mean (g/L) SD	91.8 ± 18.5
Platelets – median (× 10^9/L), range	51.5 (5-359)
LDH - median (U/L), range	384 (112-1595)
LDH, ≥ 450 U/L (N, %)	34 (43.6%)
CRP - median (g/L), range	11.4 (0.2-385)
Fibrinogen - median (g/L), range	5.1 (1.3-13)
Blasts in PB (median%, range)	4% (0-97)
Blasts in BM (median%, range)	57,5% (20-95)
De novo AML	67 (79.5%)
Secondary AML	17 (20.5%)
ELN risk group (N, %)	
Favorable	9 (11.4%)
Intermediate	54 (68.4%)
Unfavorable	16 (20.3%)
Hospitalization in COVID Hospital UCCS prior to induction therapy (N, %)	11 (13.1%)

Empirical antibiotic treatment was administered at the first sign of febrile neutropenia within an hour according to the European Society for Medical Oncology (ESMO) recommendations on febrile neutropenia management [7]. Patient history and physical examination data at admission were evaluated. Standard definitions for febrile neutropenia, sepsis, and septic shock were used [7,19,20].

Patient data were retrieved from patient histories in paper and electronic format. The patient baseline characteristics were evaluated - demographic characteristics (age, sex, smoking, Body Mass Index (BMI)), percentage of blasts in the peripheral blood sample and in the bone marrow, Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidities and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score and laboratory parameters. Cytogenetic and selected molecular characteristics of AML were analyzed. Additionally, infection source and resistance patterns of isolated bacteria were evaluated. During the COVID pandemic, according to hospital and public policy, AML patients who were found to have COVID infection were hospitalized in the COVID-Hospital UCCS, therefore we evaluated the hospitalization status of our patients. Early death (ED) was defined as death within 28 days from the start of induction chemotherapy [21].

Statistical analysis

Statistical analysis included methods of descriptive and analytical statistics. Measures of central tendency (arithmetic mean, median), measures of variability (standard deviation, minimum, and maximum value), and relative numbers were used for the descriptive statistics. Analytical statistics methods were used to compare data: Chi-square test/Fisher's exact test for categorical data, Student's t-test (for numerical data with a normal distribution), and Mann Whitney U test (for numerical data without normal distribution). Tests of univariate logistic regression were used. A $p < 0.05$

was considered statistically significant. All data and statistical analyses were conducted using IBM SPSS 25 (IBM Corp., Armonk, NY, USA).

Results

A total of 84 patients were included in our study, 48 (57.1%) were female, while the median age of the patients was 56 (18-71). The median BMI score of our selected group was 26.6 (18-53). Baseline characteristics are presented in Table 1.

Colonization of the nasal airways and pharynx was evaluated at admission, with 5 (6%) and 13 (15.5%) of patients being colonized with opportunistic pathogenic bacteria most of which were identified as *Enterococcus* spp. (46.7%), *Klebsiella* spp. (26.7%), *Acinetobacter* spp. (20%), and *Proteus* spp. (6.6%) in throat swabs, while nasal pathways were colonized by non-Methicillin-resistant *Staphylococcus aureus* (MRSA) (100%). Rectal, axillar, and inguinal swabs did not detect any significant colonization apart from normal microbiota.

Out of all patients 8 (9.8%) patients presented with no clinically apparent infection, labeled as fever of unknown origin (FUO). On the other hand, 48 (58.5%) patients had one or two documented clinically evident infectious syndromes, while 26 (31.7%) manifested with three or more of the aforementioned events. The median number of clinically documented infective syndromes in induction was 2 (0-5) per patient.

Out of 22 (26.2%) patients with apparent gastrointestinal symptoms, *Clostridium difficile* infection was diagnosed in 11 (13.2%) patients, while other causative agents of gastrointestinal infections were identified in 3 patients. All three of these patients developed *Enterococcus* spp. infection, while one of them had a concurrent *Salmonella enteritidis* infection (*Enterococcus* spp. and *Salmonella enteritidis*).

Blood cultures came back positive in 41 patients (48.8%), with a total of 56 isolates, mostly represented by *Klebsiella pneumoniae* (24, 42.8%), followed by coagulase negative *Staphylococcus* spp. (14, 25%) and *Enterococcus* spp. (10, 17.8%). Urine cultures were positive in 25 patients (29.8%). A total of 11 patients (13.1%) presented with other infection sites, most commonly wound infections (4 patients (4.8%)), whereas 9 patients had FUO (10.7%).

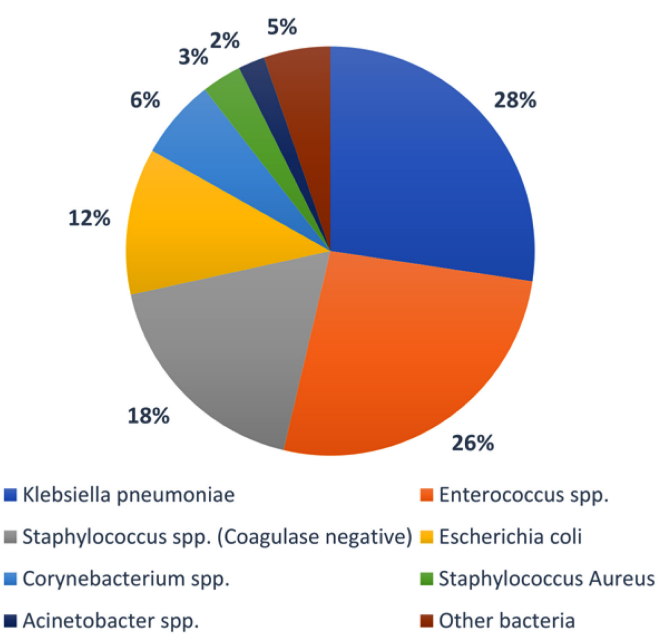
Pneumonia was diagnosed in 33 patients (39.3%). Invasive pulmonary aspergillosis was diagnosed as probable in 4 (4.8%), and likely in 11 (13.1%). In 6 cases, the causative agent was the SARS-CoV-2 virus (7.2%). The rest were 1 *Enterococcus* spp. and 1 *Acinetobacter* spp. infection (1.2% respectively) and *Klebsiella* spp. in 3 cases (1.4%) and pneumonia of unknown etiology 7 (10.7%).

The median duration of CVL placement was 17 days (5-26). CVL infections were clinically reported in 22/84 (26.5%). Positive CVL bacterial isolates were identified in 11/22 (50%) of which 7 (63.6%) were coagulase negative *Staphylococcus* spp., 3 (27.3%) were identified as *Klebsiella* spp. and there was 1 (9.1%) *Corynebacterium* spp. bacterium.

Sepsis was established in 20 (23.8%) patients during the induction treatment, while 12 (14.2%) patients required some form of oxygen support therapy (non-invasive respiratory support and invasive respiratory support in 6 (7.1%) patients respectively).

From a total of 95 samples, 52 Gram-positive bacteria (54.7%) and 43 Gram-negative bacteria (45.3%) were isolated. The isolated bacteria are presented in Figure 1.

Figure 1. Distribution of bacteria isolated from patients.



In regards to antibiotic resistance, 40.7% of patients had carbapenem-resistant isolates in at least one culture. Vancomycin-resistant *Enterococcus* (VRE) positive patients accounted for 15.5% of total patients treated. Additionally, when it comes to MDR bacteria, 10.7% patients had at least one MDR bacterial strain, 22.6% had at least one Extensively-drug resistant (XDR), and 2.4% patients had Pan-drug resistant (PDR) strains.

Among the isolated bacteria, 88% *Klebsiella* spp. isolates were resistant to carbapenems. Also, most of the isolated *Enterococcus* spp. (77.3%) were carbapenem-resistant. Of the mentioned 16 samples of *Klebsiella* spp., 2 (7.7%) were resistant to all tested antibiotics (including colistin and ceftazidime/avibactam). In addition, 14 VRE (56%) were isolated. XDR *Klebsiella* spp. dominated the isolated strains registered in 57.7% of cultures, while MDR and PDR strains were isolated in 15.4% and 7.7%, respectively. *Enterococcus* spp. was identified as MDR or XDR in 40% and 28% respectively. One *Enterococcus* spp. (4%) the isolate was resistant to Linezolid, whereas none were identified as resistant to tigecycline.

No cases of MRSA or VRSA were isolated, while all the isolated coagulase negative *Staphylococcus* spp. were susceptible to vancomycin. Antibiotic resistance patterns are showcased in Table 2.

Overall resistance to quinolones was detected in 83.8% of tested bacterial isolates, while Ceftazidime/avibactam resistance was detected in 3 isolates (21.4% of total *Klebsiella* spp. tested for this antibiotic).

In the group of patients who were found to have infections caused by MDR bacteria ECOG PS > 2 at baseline (6/30 vs 2/53) (p = 0.024) was significantly more common. The group with isolated MDR bacteria also had a significantly larger number of induction deaths (11/30 vs 9/43) (0.007) and sepsis (12/30 vs 8/50) (p = 0.016) and these patients were more likely to develop at least two infectious syndromes during induction (15/30 vs 11/52) (p = 0.007). The difference in hospitalization rates in the COVID-Hospital UCCS due to concomitant COVID infection before induction therapy (p = 0.06) and LDH ≥ 450 U/L at baseline (p = 0.07) were found to be statistically insignificant between the groups.

Early death was recorded in 20 cases (24.4%), while infection was the main contributing factor in 12/20 patients (60%). Among patients with a confirmed MDR bacterial infection, the mortality rate was recorded as 36.7%.

Factors associated with early death were secondary AML (p = 0.009), patients who presented with two or more documented clinical infections (p = 0.018), sepsis (p < 0.001), positive blood culture (p = 0.001), carbapenem resistant bacteria (p < 0.001), VRE (p = 0.013), MDR bacteria (p = 0.049).

Discussion

Patients with AML belong to a unique category of patients, owing to the distinct aggressive nature of the disease, the associated immunological deficiency, and the added weight of intensive chemotherapy protocols. This makes them candidates for life-threatening infections and other well-known complications. Infections commonly present as febrile neutropenia, however, the etiology is often unknown at the presenting symptoms. The epidemiological bacterial data in neutropenic patients with fever is important as infections can rapidly progress, leading to shock, where prompt and rapid antimicrobial therapy within one hour is necessary [11].

In our study, a slight predominance of Gram-positive bacteria was found in all isolates, in contrast to other tertiary centers, especially in developing countries, where the main share of isolated bacteria is Gram-negative [5,22]. On the other hand, a higher percentage of Gram-positive bacteria was noted in other geographical areas [6,14,23–25] According to the literature, possible explanations for the increased frequency of Gram-positive bacteria in certain centers are prophylaxis with fluoroquinolones, the use of potent chemotherapy protocols that damage mucous membranes, and the frequent use of CVL [14,22].

As reported in the study by Cernan *et al.* pneumonia seemed to be the most common site of infection both at presentation and during induction treatment (31% and 58.1% respectively) [26]. On the contrary, the Polish Adult Leukemia Group (PALG) reported a slightly

Table 2. Antibiotic resistance patterns of isolated bacteria.

Antibiotic	All bacteria (n = 95)		*Klebsiella* spp. (n = 26)		*Enterococcus* spp. (n = 25)	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Amoxicillin	10 (18.5%)	44 (81.5%)	1 (4.5%)	21 (95.5%)	7 (38.9%)	11 (61.1%)
Piperacilin/Tasobactam	1 (1.1%)	20 (95.2%)	0 (0%)	13 (100%)	0 (0%)	4 (100%)
Cephalosporins	14 (29.2%)	34 (70.8%)	3 (12%)	22 (88%)	3 (12%)	22 (88%)
Carbapenems	21 (33.3%)	42 (66.7%)	4 (15.4%)	22 (84.6%)	2 (11.1%)	16 (88.9%)
Amikacin	29 (45.3%)	35 (54.7%)	6 (25%)	18 (75%)	1 (11.1%)	8 (88.9%)
Fluoroquinolones	12 (16.2%)	62 (83.8%)	3 (11.5%)	23 (88.5%)	0 (0%)	16 (100%)
Trimethoprim/ Sulfamethoxazole	13 (28.3%)	33 (71.7%)	3 (15.8%)	16 (84.2%)	3 (15.8%)	16 (84.2%)
Chloramphenicol	12 (63.2%)	7 (36.8%)	6 (54.5%)	5 (45.5%)	6 (54.5%)	5 (45.5%)
Vancomycin	38 (73.1%)	14 (26.9%)			11 (44%)	14 (56%)
Teicoplanin					3 (50%)	3 (50%)
Linezolid					22 (95.7%)	1 (4.3%)
Tygecline			1 (11.1%)	8 (88.9%)	22 (100%)	0 (0%)
Colistin	18 (66.7%)	9 (33.3%)	14 (63.6%)	8 (36.4%)	2 (100%)	0 (0%)
Ceftazidime/Avibactam	12 (80%)	3 (20%)	11 (78.6%)	3 (21.4%)	1 (100%)	0 (0%)

lower rate of pneumonia (26%) [27]. These results compare similarly with our cohort (38.6% during induction).

When it comes to the detected bloodstream infections (BSI), our results suggest a marked difference to certain research groups – 48.8% compared to 22-27% [5,26,27], whereas particular studies demonstrate comparable rates of BSIs (47.3%) [4]. However, as observed in the available literature, the most common isolate in blood cultures were Gram-negative bacteria, namely *Klebsiella pneumoniae* [5,22,26], which is in agreement with our findings, (42.8%). Mishra *et al.,* in contrast, report an increased prevalence of *Bukholderia cepacia* and *Acinetobacter* spp. [4]. Other findings indicate a predominance of Gram-positive bacteria in blood cultures [27]. In general, *Enterococcus spp*. was the most frequently observed bacterium, in comparison to other studies where *Streptococcus viridans*, coagulase-negative *Staphylococcus*, *Escherichia coli* were the most common isolates [6,23]. In certain centers, *Enterococcus* spp. isolates were rarely described [22].

In Australia, a study was conducted in which 59.1% of all *Enterococcus spp*. isolated were VRE, compared to our finding of 56% [6]. On the other hand, Cernan *et al.* do not report a single VRE (0/8) isolated in blood cultures in their study group, however they did isolate VRE in 14 patients in colonization swabs at discharge [26].

Ghosh *et al.* in their study in India report 50% carbapenem-resistant *Enterobacteriaceae* (CRE), of which 66.7% *Klebsiella pneumoniae* are carbapenem-resistant and 6.7% colistin-resistant compared to 88% carbapenem-resistant *Klebsiella* spp. isolates in our study and 36.4% colistin-resistant. They also observed a high resistance rate to the first empiric line of antibiotics piperacillin/tazobactam and amikacin. Accordingly, the author states that it is necessary to consider changing empiric antibiotics in accordance with their data [28]. Likewise, other study groups report varying rates of carbapenem-resistant bacteria ranging from 31-85.7% [4,25,29]. However, our results point to an alarming risk of PDR bacteria development, with high resistance patterns to colistin (36.4%) and ceftazidime/avibactam (21.4%).

MRSA and VRSA were not isolated in our cohort of patients, which is in line with the low rates reported in similar studies [24,26].

Prior hospitalization in the COVID-Hospital UCCS, was not found to be associated with an increased rate of MDR bacterial infection or increased ED, however, certain studies point out an increased overall mortality in AML patients during the COVID-19 pandemic [15,16,30].

The rate of MDR bacteria varies among different populations ranging from 22-55% in India [1,5], whereas, in European centers based on colonization screening, 24% of patients were colonized with MDR bacteria, of which 12% had XDR *P. aeruginosa* strains, and 6.9% had PDR and XDR *Stenotrophomonas maltophilia* strains [26]. Additionally, Ballo *et al.* reported seemingly lower rates of CRE colonization in their cohort (13.3%) [31].

The established risk factors for CRE are exposure to previous antibiotic therapy (carbapenems), age over 65 years and hospital stay 21 days and longer [14]. While our results do not indicate a statistically significant association with age, ECOG PC > 2 was a factor for MDR bacterial infections. A possible explanation for the increase in CRE *Klebsiella* spp. could be attributed to the widespread empirical usage of carbapenems.

When it comes to prophylactic antibiotic usage, various forms of prophylaxis are applied, most commonly fluoroquinolones [24,32]. There have been controversies surrounding the effectiveness of prophylaxis. Historically, prophylaxis was associated with a better outcome in large registry studies [33,34]. However, the increased exposure to fluoroquinolones could be attributed to an increase in resistance patterns of bacteria, as demonstrated from the date in this study - all isolated bacteria (83.8%), even reaching 100% in *Enterococcus* spp. Such results correspond to other study groups [24]. Moreover, a meta-analysis conducted on a pooled total of 826 patients, of which 356 patients received levofloxacin prophylaxis demonstrated a decrease in febrile episode incidence, however, without an effect on overall survival [35].

In comparison to the findings from the Serbian Fourth National Point Prevalence Survey regarding Healthcare-associated infections, a higher percentage of pneumonias and bloodstream infections as well as a higher prevalence of CRE bacteria, especially *Klebsiella* spp. (88% compared to 35.9%) was documented. The rate of identified VRE was higher in our population as well, while VRSAs were not identified in either of these studies. The comparison is limited as the study encompassed a heterogeneous group of patients from a wide variety of wards (surgery, intensive care, general medicine, etc.). Moreover, as stated previously, AML is a state of intense immunodeficiency. However, the results of this study are consistent with the general trends of the local bacterial landscape [36].

Infections to this day present a major cause of early mortality during AML induction therapy. Our results show that among the 20 cases of patients who died during induction, 60% had an infectious etiology. This result is comparable to the results of various study groups [4,26,27]. Trecarichi *et al.* suggest an even higher mortality rate amongst patients with confirmed BSIs, rising to 52.2% in Carbapenem-resistant *Klebsiella pneumoniae* BSIs [29]. In light of this, it should be noted that the statistical analysis of our data implied that isolated CRE were a risk factor for ED.

The weakness of this study is reflected in its retrospective, single-center design on a relatively small patient group. However, this study presents a valuable insight on novel shifts in resistance patterns of MDR bacteria in a homogenous AML group.

Conclusions

Infections remain a major challenge in the treatment of AML. Our work demonstrates that the frequency of infections in this population is high, especially with MDR and XDR strains of *Klebsiella* spp. and *Enterococcus* spp., which are accompanied by high rates of ED. In regards to the ever more prevalent presence of MDR bacteria, it is important to have knowledge of epidemiological data both from a single center, as well as more nationwide registries. Daily microbiological surveillance and adequate de-escalation of antimicrobial therapy are necessary to limit this trend of infection and resistance.

Corresponding author

Lazar Trajković, MD
Clinic of Hematology,
University Clinical Centre of Serbia
Pasterova 2, Belgrade, Serbia.
Email: trajkovic.lazar33@gmail.com

Conflict of interests

No conflict of interests is declared.

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