Efficacy of Cefoperazone-Sulbactam as Empirical Monotherapy Therapy for Febrile Neutropenia in Children with Solid Tumors and Lymphomas

Lenfoma ve Solid Tümörlü Çocuklarda Febril Nötropenide Sefaperazon-Sulbaktam Monoterapisinin Etkinliği

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ABSTRACT

Objective: Monotherapy with a beta lactam or a cephalosporin has become the standard of care for the treatment of febrile neutropenia (FEN). We aimed to evaluate the efficacy of cefoperazone/sulbactam (CS) as empirical monotherapy for febrile neutropenia in children with solid tumors and lymphomas.

Material and Methods: Children with FEN received cefaperazone-sulbactam (80 mg/kg/day, every 8 hours). Treatment responses (a) successful, complete resolution of all signs and symptoms of infection at 72 hours and after 7 days of CS treatment; (b) success with modification, change of therapy for viral, parasitic or fungal infection or addition of glycopeptides; (c) failure was defined as the emergence of a new or resistant infection, treatment-resistant bacteremia, the need to switch to carbapenems.

Results: Our study included 157 patients and 350 febrile neutropenia episodes. The most common diagnoses were osteosarcoma (35%), Ewing sarcoma (30%), non-hodgkin lymphoma (13%) and rhabdomyosarcoma (9%), respectively. The origin of fever could not be determined in 223 (64%) of FEN episodes, 79 (22%) had microbiologically documented infection (MDI), and 48 (14%) had clinically documented infection (CDI). The success rate was 65% (229), the success rate with modification was 9% (31) and the failure rate was 26% (90). SC monotherapy was successful in 33% of attacks with MDI and in 60% of attacks with CDI. However, SC monotherapy was successful in 82% of febrile episodes of unknown origin.

Conclusion: Cefoperazone/sulbactam is effective and safe in febrile neutropenic children with solid tumors and lymphomas for monotherapy.

Key Words: Cancer, Cefoperazone, Child, Febrile neutropenia, Sulbactam

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ÖZ

Amaç: Febril nötropeninin tedavisinde beta laktam veya bir sefalosporin ile monoterapi, standart haline gelmiştir. Bu çalışmada solid tümörlü ve lenfomalı çocuklarda febril nötropeninin ampirik tedavisi olarak sefoperazon/sulbaktamın (SS) etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Febril nötropenik çocuk hastalara sefaperazon-sulbaktam (80 mg / kg / gün, 8 saatte bir) başlandı. Tedavi yanıtları (a) başarılı, 72. saatte ve 7 günlük SS tedavisinden sonra enfeksiyonun tüm belirti ve semptomlarının tamamen düzelmesi; (b) modifikasyon ile başarılı, viral, parazitik veya mantar enfeksiyonu için tedavi değişikliği veya glikopeptid ilavesi; (c) başarısızlık, yeni veya dirençli bir enfeksiyonun ortaya çıkması, tedaviye dirençli bakteriyemi, karbapenemlere geçme veya aynı spektrumda bir antibiyotik ekleme ihtiyacı olarak tanımlandı.

Bulgular: Yüz elli yedi hastaya ait 350 febril nötropeni atağı (K: 73, E: 84, ortanca yaş: 11.8 yıl (0.6-18)) kaydedildi. En sık tanılar sırasıyla osteosarkom (%35), Ewing sarkomu (%30), non-hodgkin lenfoma (%13) ve rabdomyosarkomdu (%9). Ortanca mutlak nötrofil sayısı 60/mm^3 (0-800) ve nötropeni süresi 7 gün (3-60)'dı. Ortanca tedavi süresi 7 gündü (3-30). FEN ataklarının 223'ünde (%64) ateşin kaynağı tespit edilemedi, 79'unda (%22) mikrobiyolojik dokümante enfeksiyon (MDE) vardı ve 48'inde (%14) klinik dokümante enfeksiyon mevcuttu (KDE). Başarı oranı %65 (229), modifikasyon ile başarı oranı % 9 (31) ve başarısızlık oranı %26 (90)'dı. Sefoperazon/sulbaktam monoterapisi MDE olan atakların %33'ünde, KDE olan atakların %60'ında başarılı oldu. Ancak SS monoterapisi nedeni bilinmeyen ateşli atakların %82'sinde başarılı oldu.

Sonuç: Sefoperazon/sulbaktam, solid tümör ve lenfomalı çocuklarda nötropenik ateşin tedavisinde monoterapi olarak etkili ve güvenlidir.

Anahtar Sözcükler: Kanser, Sefoperazon, Çocuk, Febril nötropeni, Sulbaktam

INTRODUCTION

Fever is a common sign of an infection in neutropenic patients in pediatric oncology. If left without treatment, destructive complications of bacterial sepsis may occur. Therefore, febrile neutropenia (FEN) should be treated as a medical emergency (1).

An optimal initial antibiotic treatment should have a wide spectrum including but not restricted to Pseudomonas, be bactericidal, have low potential of side effects and the treatment options should be based on the microbiological data of the centers (1,2).

In earlier years, combination therapies in FEN were accepted as standard treatment method because of their antimicrobial synergy to gram-negative bacteria and decreased resistance. Mostly preferred combination regimen was wide-spectrum β-lactam antibiotic and amikacin (3-5). However, after the development of 3rd and 4th generation cephalosporins such as ceftazidime, cefepime and carbapenems, monotherapy has proven to be safe to use in FEN (3,6). Antibiotic monotherapy has attractive aspects such as easy administration, low cost, reduced toxicity especially due to aminoglycosides (1). Another option for empirical treatment of infections in FEN is β-lactam/β-lactamase inhibitor combinations. They have a broad spectrum including both gram-negative and gram-positive bacteria and also prevent resistance to β-lactam alone (7). Sulbactam is a molecule given in combination with β-lactam antibiotics to eliminate the effects of β-lactamase. By the addition of sulbactam to cefoperazone, a third- generation cephalosporin with a restricted effect on gram-negative bacteria, it broadens its spectrum of action (8,9). In this retrospective study, we aimed to assess the efficacy of cefoperazone-sulbactam (CS) as empirical monotherapy for FEN in pediatric cancer patients with solid tumors.

MATERIALS and METHODS

We reviewed the medical records of pediatric cancer patients that experienced episodes of febrile neutropenia between October 2004 and August 2016. Children with neutropenic fever (age ≤ 18years) hospitalized at Ankara Oncology Hospital for lymphomas and solid tumors were included in the study. Informed written consent was obtained from all patients. Fever was defined as either a single axillary temperature of ≥ 38°C or sustained temperature over 1 hr. of ≥ 37.5°C. Neutropenia was defined as an absolute neutrophil count (ANC)≤ 500 cells/mm^3 or an ANC with expected fall to ≤500 cells/mm^3 within 48 hr (2).

Informed consent was obtained from all enrolled patients and study was approved by the ethics committee at Ankara City Hospital and carried out by the Declaration of Helsinki principles and all applicable regulations (E2-21-604).

Evaluation before treatment

After a detailed medical history and complete physical examination, at least two venous blood cultures (both peripheral vein and central venous catheter (CVC) if present), urine culture and culture from any suspected local sites were obtained. Blood samples were collected for complete blood count, liver and kidney function tests, and urine analysis was also done. A chest X-ray was performed for patients whom presented with respiratory symptoms. The remission status, white blood cell count, the absolute neutrophil count (ANC), duration of neutropenia, number of febrile days, granulocyte-colony stimulating factor use were recorded.

Classification of febrile neutropenia episodes

The FEN episodes were divided into three groups as clinically documented infection (CDI), microbiologically documented infection (MDI) or fever of unknown origin (FUO). Clinically documented infection was described when there was a focus of infection on physical examination without a pathogen documented. Microbiologically documented infection was described as the documentation of a microorganism. Fever of

unknown origin was described when there was no clinical or microbiologic sign of infection in a FEN episode.

Antibacterial treatment

Empirical CS 80 mg/kg/day was promptly initiated to all patients in three divided doses. All patients were hospitalized. Patients were monitored daily until being afebrile and ANC ≥500 cells/mm^3. If fever persisted >38.0^{o}C at 72 hours of treatment with no documented microorganism or the patient deteriorated, treatment was switched to carbapenems and glycopeptides were added. If a resistant bacterium was detected and the patient had no clinical improvement, antibiotherapy was planned according to antibiogram results. If fever persisted on the 5-7th day of the FEN episode, liposomal amphotericin-B at 3 mg/kg/dose was added. Treatment continued if fever disappeared or the patient clinically improved despite fever, no infectious agent was detected and neutropenia started to recover. If the patients improved clinically, treatment was discontinued after 5 days without fever, even if they were still neutropenic.

Evaluation of the Treatment

Treatment responses were defined as (a) successful treatment, complete resolution of all signs and symptoms of infection at 72 h and after 7 days of treatment with CS; (b) successful with modification, the need for treatment change for a viral, parasitic or fungal infection, or addition of glycopeptide; or (c) failure, emergence of a new infection, a resistant microorganism, therapy resistant bacteremia, the need to switch to carbapenems or add an antibiotic with the same spectrum.

Statistical analysis

Data were analyzed with IBM SPSS V23. Compliance with normal distribution was examined by Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare quantitative variables that were not normally distributed according to groups. Analysis results are median for quantitative data. Categorical data were presented as frequency and percentage, with deviation and median (minimum - maximum). p-values of < 0.050 were defined as significant.

RESULTS

Patient Characteristics

From October 2004 to August 2016, a total of 350 FEN episodes were recorded in 157 (73 female, 84 male) pediatric cancer patients. The median age was 11.8 years (0.6-18). Median absolute neutrophil count and duration of neutropenia were 60/mm^3 (0–800) and 7 days (3–60). The median time of antibiotherapy was 7 days (3-30). Underlying diagnoses were osteosarcoma (35%), Ewing's sarcoma (30%), non-hodgkin lymphoma (NHL) (14%) rhabdomyosarcoma (9%) and other (12%) (Table I).

Characteristics of febrile episodes

Of the 350 episodes, 113 (32%) were during induction therapy, 114 33%) were during partial remission, 87 (25%) were during the treatment for relapsed disease, and the remaining 36 (10%) were during remission treatment. Prophylactic antibiotics were not administered to any patient.

Table I: Characteristics of Patients and Febrile Neutropenia Episodes

Total number of episodes Total number of patients	Cefoperazone-sulbactam (n:350) (n:157)
Age (years)	
Range	0.6-18
Median	11.8
Sex*	
Male	73 (54)
Female	84 (46)
Primary disease*	
Osteosarcoma	55 (35)
Ewing's Sarcoma	47 (30)
NHL	22 (14)
RMS	14 (9)
Other	19 (12)
Neutrophil [count cells/mm^3*	
Range	0-800
<100	164 (47)
100-500	102 (29)
>500	8 (2)
Unknown	76 (22)
WBC(×10^9/L)†	450 (0-2600)
Remission status*	
In remission	36 (10)
Not in remission	314 (90)
Grade 3-4 mucositis	41 (12)
GCSF use	289 (82)
Central venous catheter	
Yes	164 (47)
No	186 (53)

** n (%), † median (min.–max.)*

The origin of fever could not be detected in 223 (64%) episodes (FUO), microbiologically documented infection was present in 79 (22%) episodes (MDI), and infection was clinically documented (CDI) in 48 (14%). As shown in Table II, the two most common sites of infection were gastrointestinal tract infection [48% (n = 23)] and respiratory tract infection including pneumonia [45% (n= 22)].

In 60% of the 79 MDI episodes a single gram-positive bacterium, in % 36 of episodes a single gram-negative bacterium and in 4% fungi were isolated (Table II). Polymicrobial organisms were not documented.

Treatment Responses

Table III presents the outcome of empirical CS regimen. Modifications were needed in 121 (35%) of the 350 episodes. The overall success rate was 74%, of which 65% were successful without modification and 9% were successful with modification. The most commonly used agents for modification were carbapenems and glycopeptides. The use of aminoglycosides alone or in combination was 2.5%. No death

Table II: Documentation of infections in febrile neutropenia episodes

	n=350
Clinically documented	48 (14%)
URTI	7
LRTI	15
Skin/soft tissue infection	3
Gastrointestinal infection	23
Anal abcess	16
Neutropenic enterocolitis	3
Other abdominal infections	4
Microbiologically documented	79 (22%)
Gram positive	47 (60%)
S. epidermidis	25
MRSA	13
Streptococcus pneumoniae	1
Kocuria kristinae	3
Enterococcus spp	5
Gram negative	29 (36%)
Escherichia coli	13
Klebsiella spp	6
Proteus spp	4
Salmonella spp	1
Pseudomonas spp	2
Serratia	1
Enterobacter spp	2
Fungus	3 (4%)
Candida spp	3
Fever of unknown origin	223 (64%)

URTI: *Upper respiratory tract infections,* ***LRTI:*** *Lower respiratory tract infections,* ***MRSA:*** *Methicillin resistant Staphyloccocus aureus*

Table III: Outcome of treatments of febrile neutropenic episodes

Total number of episodes	Cefoperazone-sulbactam (n=350)
Duration of neutropenia	3-60 (median 7 days)
Duration of fever	1-40 (median 2 days)
Duration of antibiotic treatment	3-30 (median 7 days)
The results of treatment	
Successful	229 (65%)
Successful with modification	30 (9%)
Unsuccessful	91 (26%)
Adverse events	None
Modifications	121 (35%)
Carbapenem+Glycopeptides	48
Carbapenem+Glycopeptides+Antifungals	22
Glycopeptides	28
Carbapenem	13
Amikacin	7
Amikacin + Antifungals	2
Glycopeptides + Antifungals	1
Death	None

occurred during the FEN episodes. The only factor affecting treatment success was the presence of microbiologically documented infection ($p < 0.050$). The success rate was 33% in MDI and 60% in CDI episodes. In FUO, the success rate was the highest with 82% of 223 episodes. A total of 41 (12%) grades 3-4 mucositis were observed in all 350 FEN episodes. One patient had severe gastrointestinal bleeding not treatment-related but due to disease involvement. No other adverse effects were observed.

DISCUSSION

In current pediatric guidelines, monotherapy with an antipseudomonal β-lactam, a fourth- generation cephalosporin or carbapenem is highly recommended due to its efficacy, safety, and fewer side effects in high-risk febrile neutropenia as the initial treatment (10). In a recent systematic review, monotherapy in FEN has been shown to be at least as effective and safe as aminoglycoside-containing combination regimens (11). Several clinical studies have explored the efficacy and safety of CS in FEN both in adults and pediatrics. Most of these studies compared the CS with other agents such as piperacillin/tazobactam or carbapenems and CS was found to be as effective as the others (9,12-16). A recent meta-analysis showed that the clinical efficacy and tolerability of CS in the treatment of febrile neutropenia is as high as the drugs compared to it (17). Cefoperazone-sulbactam is one of the essential drugs to be used empirically according to Turkish febrile neutropenia guidelines (18). Cefoperazone-sulbactam has been used as monotherapy for febrile neutropenia for a long time in our center. Our results show that CS can be used safely without the need for a combination in febrile neutropenia. The overall success rate in our study (74%) was comparable to the success rate in literature that vary between %53-88.

FUO rates in our study (64%) were similar to other studies reported to range from 44% to 80% (9,14-16,19). The group in which CS was most effective was FUO with overall success rate 84%. Clinically documented infection rate in our study was 14%, which was a relatively low rate. Very variable CDI rates such as 12.5%, 26%, 32% and 59% have been reported in the literature, and this may be due to the fact that complications such as severe mucositis were considered in the CDI category in some studies (6,9,14,20). In contrast to the literature, where respiratory tract infections are the most common, gastrointestinal tract infections, especially anal abscess were the leading among in CDI group in our study (21,22). This can be related to social economic situations in Türkiye and recurrent episodes with the same clinical findings in some patients.

In the last 3 decades, a worldwide change from gram negatives to gram positives has been observed in infectious agents isolated in febrile neutropenia (23). Studies in our country have also shown that gram positive bacteria are predominantly isolated in FEN (6,14,24). This is because of frequent use of central venous catheters and more intensive chemotherapy in childhood cancers (25). Central venous catheters are routinely

used in our center, and in 164 out of 350 episodes, patients had catheters. Moreover, 64 of the 79 MDI episodes occurred in patients with catheters and 84% of these were catheter-related bloodstream infections. These data in our study highlight the importance of catheter care. The MDI rate in our study was 22%, similar to the rates in the literature (15.5-24%). The group in which CS was least effective and required the most modification was MDI (success rate %33). Considering the resistance patterns of the isolated microorganisms, it is seen that 60% of patients in MDI group had gram positive growth and they are mostly resistant to methicillin or penicillin. In this case, even if other antipseudomonal agents were used instead of CS in empirical monotherapy, failure could be seen in the MDI group. For this reason, failure cannot be attributed to CS alone.

Consistent with the IDSA 2010, the most common bacterial species isolated in our study are gram-positives, and 53% of them were coagulase-negative staphylococci (2).

In our study, 65% of the patients had primary bone sarcoma and only %14 had non-Hodgkin's lymphoma but interestingly the modification was required most frequently in patients with non-Hodgkin's lymphoma (26 of 42 episodes). The probable reason for this was that 45% of patients with NHL had severe mucositis during FEN episodes. Although patients with osteosarcoma received methotrexate at high doses of 12 gr/m^2, the reason for the relatively low incidence of mucositis may be the intensive oral care prophylaxis we apply. The modification rate was significantly higher in patients with neutropenia lasting more than 10 days (28% vs 74%, p <0.001) and in patients with severe mucositis (30% vs 65%, p<0.001). The overall modification rate (35%) is similar to the literature, with no deaths during episodes.

To our knowledge, this is the study with the largest number of FEN episodes in which CS was used as monotherapy in children. Our results show that, cefoperazone/sulbactam is both effective and safe as empirical therapy in febrile neutropenic children with solid tumors and lymphomas. Therefore, CS may be preferred for monotherapy in FEN in a developing country due to its negligible side effect profile, low cost compared to its counterparts, and successful overcoming of most episodes.

This study has some limitations. First, since this is not a randomized controlled trial, we compared the results with the literature. This study reflects the results of a single center. It would be valuable if we had the opportunity to do cost effective analysis. This may be possible with larger multicenter studies.

In conclusion, CS is effective and safe in febrile neutropenic children with solid tumors and lymphomas for empirical monotherapy. No severe toxicity was observed.

REFERENCES

1. Ardura M.I KAY. Infectious Complications in Children with Underlying Malignancy. In: Blaney S.M HLJ, Adamson PC, editor. Pizzo and Poplack's Pediatric Oncology. EIGHT ed. Philadelphia: Wolters Kluwer Health 2021.
2. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 2011;52:e56-93.
3. Anoshirvani AA, Zarinfar N, Rafiee M, Zamani Z. Effect of combination therapy of ceftazidime/amikacin and monotherapy with imipenem on the treatment of fever and neutropenia in patients with cancers. Open Access Maced J Med Sci 2018;6:1423-30.
4. Andreatos N, Flokas ME, Apostolopoulou A, Alevizakos M, Mylonakis E. The dose-dependent efficacy of cefepime in the empiric management of febrile neutropenia: a systematic review and meta-analysis. Open Forum Infect Dis 2017;4: ofx113.
5. Lee NH, Kang JM, Lee JW, Huh HJ, Lee NY, Yoo KH, et al. Cefepime versus cefepime plus amikacin as an initial antibiotic choice for pediatric cancer patients with febrile neutropenia in an era of increasing cefepime resistance. Pediatr Infect Dis J 2020;39:931-6.
6. Kebudi R, Kizilocak H. Febrile neutropenia in children with cancer: approach to diagnosis and treatment. Curr Pediatr Rev 2018;14:204-9.
7. Horita N, Shibata Y, Watanabe H, Namkoong H, Kaneko T. Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis. Clin Microbiol Infect 2017;23:723-9.
8. Xin X, Jian L, Xia X, Jia B, Huang W, Li C, et al. A multicentre clinical study on the injection of ceftriaxone/sulbactam compared with cefoperazone/sulbactam in the treatment of respiratory and urinary tract infections. Ann Clin Microbiol Antimicrob 2013;12:38.
9. Karaman S, Vural S, Yildirmak Y, Emecen M, Erdem E, Kebudi R. Comparison of piperacillin tazobactam and cefoperazone sulbactam monotherapy in treatment of febrile neutropenia. Pediatr Blood Cancer 2012;58:579-83.
10. Lehrnbecher T, Robinson PD, Ammann RA, Fisher B, Patel P, Phillips R, et al. Guideline for the Management of Fever and Neutropenia in Pediatric Patients With Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update. J Clin Oncol 2023;41:1774-85.
11. Robinson PD, Lehrnbecher T, Phillips R, Dupuis LL, Sung L. Strategies for empiric management of pediatric fever and neutropenia in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review of randomized trials. J Clin Oncol 2016;34:2054-60.
12. Horita, N, Shibata Y, Watanabe H, Namkoong H, Kaneko T. Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis. Clin Microbiol Infect 2017;23:723-9.
13. Aynioglu A, Mutlu B, Hacihanefioglu A. A comparison of the efficacy of piperacillin-tazobactam and cefoperazone-sulbactam therapies in the empirical treatment of patients with febrile neutropenia. Rev Esp Quimioter 2016;29:69-75.
14. Demir HA, Kutluk T, Ceyhan M, Yağcı-Küpeli B, Akyüz C, Cengiz B. Comparison of sulbactam-cefoperazone with carbapenems as empirical monotherapy for febrile neutropenic children with lymphoma and solid tumors. Pediatr Hematol Oncol 2011;28:299-310.
15. Demirkaya M, Celebi S, Sevinir B, Hacımustafaoglu M. Randomized comparison of piperacillin-tazobactam plus amikacin versus cefoperazone-sulbactam plus amikacin for management of febrile neutropenia in children with lymphoma and solid tumors. Pediatr Hematol Oncol 2013;30:141-8.
16. Ponraj M, Dubashi B, Harish BH, Kayal S, Cyriac SL, Pattnaik J, et al. Cefepime vs. cefoperazone/sulbactam in combination with amikacin as empirical antibiotic therapy in febrile neutropenia. Support Care Cancer 2018;26:3899-908.
17. Lan SH, Chang SP, Lai CC, Lu LC, Tang HJ. Efficacy and safety of cefoperazone-sulbactam in empiric therapy for febrile neutropenia:

A systemic review and meta-analysis. Medicine (Baltimore) 2020;99:e19321.

18. Febrile Neutropenia Study Group. Guidelines for diagnosis and treatment of neutropenic patients. Flora 2004;9:5-28.
19. Kar YD, Özdemir ZC, Bör Ö. Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients. Turk Pediatri Ars 2017;52:213-20.
20. Uygun V, Karasu GT, Ogunc D, Yesilipek A, Hazar V. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer 2009;53:610-4.
21. Altınel E YN, Işık P, Özkasap S, Bay A, Kara A. Evaluation of febrile neutropenia in children with acute leukemia. Turkish J Pediatr Dis 2012;6:93-100.
22. Meena JP, Brijwal M, Seth R, Gupta AK, Jethani J, Kapil A, et al. Prevalence and clinical outcome of respiratory viral infections among children with cancer and febrile neutropenia. Pediatr Hematol Oncol 2019;36:330-43.
23. Alali M, David MZ, Danziger-Isakov LA, Elmuti L, Bhagat PH, Bartlett AH. Pediatric febrile neutropenia: change in etiology of bacteremia, empiric choice of therapy and clinical outcomes. J Pediatr Hematol Oncol 2020;42:e445-e51.
24. Özdemir ZC, Koç A, Ayçiçek A. Microorganisms isolated from cultures and infection focus and antibiotic treatments in febrile neutropenic children from Şanlıurfa, Türkiye. Turk J Pediatr 2016;58:47-53
25. Perdikouri EIA, Arvaniti K, Lathyris D, Apostolidou Kiouti F, Siskou E, Haidich AB, et al. Infections due to multidrug-resistant bacteria in oncological patients: insights from a five-year epidemiological and clinical analysis. Microorganisms 2019;7:277.