# A change for the antibacterial treatment policy to decrease carbapenem consumption at a haematopoietic stem cell transplantation centre

**Gökhan Metan[1], Leylagül Kaynar[2], Nuran Yozgat[3], Ferhan Elmalı[4], Cemile Altay Kürkçüoğlu[5], Emine Alp[1,5], Mustafa Çetin[2]**

[1]Departments of Infectious Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey
[2]Hematology, Erciyes University Faculty of Medicine, Kayseri, Turkey
[3]Hospital Pharmacy, Erciyes University Faculty of Medicine, Kayseri, Turkey
[4]Biostatisitics, Erciyes University Faculty of Medicine, Kayseri, Turkey
[5]Infection Control Committee5, Erciyes University Faculty of Medicine, Kayseri, Turkey

## SUMMARY

After experiencing a high rate of carbapenem-resistant Gram-negative bacilli infections in febrile neutropenic patients, a two-stage intervention was introduced in the haematopoietic stem cell transplantation (HSCT) centre. During the first eight months of 2014, carbapenems remained the first choice for the empirical treatment of febrile neutropenia while the use of piperacillin/tazobactam (TZP) was encouraged in patients with stable clinical condition. When blood cultures were reported as negative and the patient was clinically stable the carbapenem/TZP treatment was stopped regardless of continuous fever and neutrophil count. From October 2014, TZP (with prolonged infusion) with or without amikacin replaced carbapenems as the first line therapy of neutropenic fever except for high-risk patients previously known as colonized or infected with extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, who presented with severe sepsis, septic shock or nosocomial pneumonia, and recently transferred from the intensive care unit with a high endemicity of multidrug-resistant Gram-negative bacilli. Vancomycin or teicoplanin was used when there was suspicion of septic shock or detection of severe mucositis and central-line associated bacteraemia. The antibacterial therapy was escalated or de-escalated in culture-positive patients according to the antimicrobial susceptibility reports and clinical progress. Daily defined dosages (DDD) per 1000 patient days were calculated for all antibiotics by the hospital pharmacist for each year. A total of 913 admissions with 11,544 patient-days were followed in 2013; and 1,072 admissions with 11,843 patient-days were followed in 2014. The rate of ESBL production in *Enterobacteriaceae* bacteraemia was as 31.8% in 2013 and 47.3% in 2014. All staphylococci isolated from blood culture were methicillin-resistant for both years. All *Enterococcus faecium* isolates but one from blood cultures were resistant to ampicillin. The number of the patients who died during hospitalization was 24 in 2013, and 17 patients died in 2014. The DDDs/1000 patient days for imipenem, meropenem, vancomycin, daptomycin, linezolid, piperacillin/tazobactam and amikacin in 2013 and 2014 were respectively as follows; 201 *vs* 19 ($p<0.001$); 1,578 *vs* 1,092 ($p<0.001$); 533 *vs* 251 ($p<0.001$); 56 *vs* 14 ($p<0.001$); 76 *vs* 26 ($p<0.001$); 157 *vs* 254 ($p<0.001$); and 5 *vs* 41 ($p<0.001$). While there was a decreasing trend for consumption of teicoplanin (205 versus 159) and colistin (188 versus 254) , this was not statistically significant. Our study showed that a febrile neutropenia pathway guided by local epidemiology and international guidelines can reduce the use of antibiotics in haematological cancer or HSCT patients. The sustainability of such an intervention requires strong multidisciplinary cooperation.

*Keywords*: antibiotic resistance, antibiotic stewardship, stem cell transplantation, haematology.

## INTRODUCTION

Neutropenic fever is a life-threatening complication for patients receiving haematopoietic stem cell transplantation (HSCT). The high

*Corresponding author*
Gökhan Metan
E-mail: gokhanmetan@gmail.com

incidence of extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* bacteraemia in febrile neutropenic patients is of concern [1]. Therefore, carbapenems became the first line agent for the empirical treatment of neutropenic fever in our center [2]. The increasing rate of consumption of carbapenems caused a collateral damage as high incidence of carbapenem resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the haematology wards and SCT center [2, 3]. Moreover, carbapenem resistant *Klebsiella pneumoniae* also emerged at the institution without any reliable treatment options [4]. Here, we want share the results of a febrile neutropenia pathway guided by local epidemiology and international guidelines which allowed to decrease the consumption of carbapenems in a setting with high rate of ESBL producing *Enterobacteriaceae* bacteraemia.

## PATIENTS AND METHODS

Erciyes University Hospital is a 1300-bed tertiary centre with a 38-bed HSCT center. An infection control programme has been established in the HSCT centre since 2008. An infection control nurse visits all patients daily and patients are followed up to discharge for any nosocomial infections diagnosed according to the Centre for Disease Control and Prevention (CDC) criteria. All patients with suspicion of infection are evaluated by an infectious diseases (ID) physician with at least ten years of experience. The ID physician who worked at the HSCT center changed every month. Therefore, the type of and the duration of the antibacterial therapy were individual according to the attending ID physician. At October 2013, an ID physician was permanently assigned to the HSCT center. A strict antibiotic usage program was structured with the agreement of haematology physicians. Levofloxacin prophylaxis remained as the antibacterial prophylaxis for all patients receiving allogeneic HSCT. At the first eight months of 2014, carbapenems remained the first choice for the empirical treatment of febrile neutropenic patients while the use of piperacillin/tazobactam (TZP) was encouraged in patients with stable clinical condition. However, if blood cultures were reported as negative and patient was clinically stable the carbapenem or TZP treatment was stopped regardless of continuous fever and neutrophil count according to the European guideline (available at http://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/ECIL4 2011 Bacterial resistance in Haematology.pdf.). Increase in the C-reactive protein (CRP) levels or clinical deterioration triggered to initiate a new antibacterial treatment episode for neutropenic patients. From October 2014, TZP (with prolonged infusion) with or without amikacin replaced carbapenems as the first line therapy of neutropenic fever except for the patients previously colonized or infected with ESBL producing or TZP/amikacin resistant Gram negative bacilli, presented with severe sepsis/septic shock or nosocomial pneumonia, recently transferred from intensive care unit with a high endemicity of multidrug resistant Gram negative bacilli and experienced TZP during the last 30 days. Vancomycin/teicoplanin was used when suspicion of septic shock or detection of severe mucositis and central-line associated bacteraemia. Glycopeptides were stopped if blood cultures did not yield Gram positive bacteria and the patient was clinically stable. Colistin was reserved for patients who were already known as colonized or previously infected with carbapenem resistant Gram negative bacilli or recently transferred from intensive care unit with an endemicity of *Acinetobacter baumannii*. The antibacterial therapy was escalated or de-escalated in culture positive patients according to the antimicrobial susceptibility reports and clinical progress. Appropriateness of antibacterial therapy was assessed everyday by the haematology team and at least three times a week by ID physician regularly (and whenever required according to the culture results or acute changes in clinical situation of the patient).

Daily defined dosages (DDD) per 1000 patient days were calculated for all antibiotics by the hospital pharmacist for each year. The DDD for each antibiotic was compared for 2013 and 2014 by using chi-square test, and Benfori z rate was calculated to analyse the statistical difference. All statistical analyses were performed with SPSS software for Windows (version 15.0; SPSS, Chicago, IL).

## RESULTS

A total of 913 admissions with 11,544 patient days were followed in 2013; and 1,072 admissions with 11,843 patients days were followed in 2014. A to-

tal of 71 allogeneic HSCT was performed in 2013, and 56 allogeneic HSCT was performed in 2014. Ninety patients underwent autologous HSCT in 2013, and 69 patients underwent autologous HSCT in 2014. The number of the patients who died during hospitalization was 24 in 2013, and 17 patients died in 2014.

The rate for nosocomial pneumonia and central-line associated bloodstream infection (CLABSI) were as 0.95/1000 patient days and 7.29/1000 catheter days in 2013. In 2014, the rate for nosocomial pneumonia was 1.6/1000 patient days and 8.05/1000 catheter days for CLABSI.

Twenty-five patients with vancomycin resistant enterococcus (VRE) colonization were detected in 2013, while VRE colonization was detected in 12 patients in 2014. All *Enterococcus faecium* (n=2 in 2013, n=7 in 2014) isolates but one from blood cultures were resistant to ampicillin and vancomycin resistant *E. faecium* bacteraemia was detected in one patient in 2014. All staphylococci isolated from blood cultures were methicillin resistant for both years. Carbapenem resistant *Klebsiella pneumoniae* (CRKP) colonization was detected in 8 patients in 2013, and 14 patients with CRKP colonization were detected in 2014. The rate of ESBL production in *Klebsiella pneumoniae* bacteraemia was as 45.5% (5 out of 11) in 2013 and 66.6% of *K. pneumoniae* isolated from blood cultures (8 out of 12) was ESBL producers in 2014. ESBL production was detected in 27.3% (9 out of 33) of *Escherichia coli* bacteraemia in 2013. This rate increased to 38.5% (10 out of 26) in 2014.

The DDDs/1000 patient days for imipenem, meropenem, vancomycin, daptomycin, linezolid, piperacillin/tazobactam and amikacin in 2013 and 2014 were as follows; 201 *vs* 19 ($p<0.001$); 1,578 *vs* 1,092 ($p<0.001$); 533 *vs* 251 ($p<0.001$); 56 *vs* 14 ($p<0.001$); 76 *vs* 26 ($p<0.001$); 157 *vs* 254 ($p<0.001$); and 5 *vs* 41 ($p<0.001$). While there was a decreasing trend for consumption of teicoplanin (205 versus 159) and colistin (188 versus 254) , this was not statistically significant.

## DISCUSSION

Effective antimicrobial stewardship is an essential step to control antibiotic resistance. In our center, the susceptibility rate of TZP was 78.3% for *Escherichia coli*, 75% for *Klebsiella pneumoniae*, and 86.7% for *Pseudomonas aeruginosa* isolated from patients with haematological cancer or HSCT, and we were not able to show the impact of the type of empirical therapy on mortality in neutropenic patients when we started the intervention [2, 5]. TZP plus amikacin was reported to have the similar effectivity when compared with imipenem or meropenem in the empirical treatment of febrile neutropenia [6-8]. A *post-hoc* analysis reported similar efficacy of TZP and carbapenems in the treatment of ESBL producing *E. coli* [9]. These data encouraged as to change our approach for the initial management of febrile neutropenia. As pharmacokinetics of piperacillin can exhibit significant differences in febrile neutropenic patients, we preferred continuous infusion [10]. The resistance rates for TZP and amikacin should be followed cautiously in centers sharing similar febrile neutropenia management algorithms. Also, patients with high risk for infections with multidrug resistant Gram negative bacilli should be identified promptly [11]. In a center with high rate of TZP resistance, imipenem was superior than TZP for empirical treatment of febrile neutropenia in patients receiving HSCT regarding defervescence of fever within 48 h and switch the empiric antibiotic to treat bacteraemia [12].

A previous prospective double-blind randomized controlled study failed to show any benefit of empirical vancomycin therapy in persistently febrile neutropenic patients with cancer regarding to the time to defervescence, empirical addition of amphotericin B, and additional episodes of gram-positive bacteraemia [13]. Empirical vancomycin is no longer recommended if clinical or microbiological evidence of resistant Gram positive bacilli infection is not present in patients with stable clinical condition but have persistent fever [14]. Implementation of certain indications for empirical vancomycin therapy in febrile neutropenia pathway was found to be related with higher rate of appropriate use of vancomycin [15]. We were not able to identify the appropriateness of glycopeptide usage for each patient, but the consumption of glycopeptides was significantly reduced by strictly implementing the guidelines to our daily clinical practice.

One of the important debates for the treatment of febrile neutropenia is the duration of antibacterial therapy in patients without any proven infection but have prolonged neutropenia. Observational studies did not show any difference between

continuation and discontinuation of antibacterial therapy during persistent neutropenia regarding breakthrough bacterial infections and bacterial infection related mortality [16]. We adapted our daily practice to the recent European guidelines, that recommend to discontinue empiric therapy in clinically stable patients without any culture or clinically evidenced infection [11]. We stopped the empirical antibiotics if the patient did not have fever ≥72 hours and blood cultures were negative. Thoracic computed tomography (and other radiological investigations when clinically indicated), galactomannan antigen testing, and repeat blood cultures were performed in patients with fever ≥72 hours. CRP levels were measured three times a week. If the patient was clinically stable and all diagnostic tests including clinical assessment did not assign an infection source, empirical antibiotics were stopped even in case of continuous fever and neutropenia. Secondary quinolone prophylaxis was started in patients undergoing HSCT, although, the evidence for this approach has very low quality [14]. Serial Monitorization of CRP levels was helpful for the discontinuation decision in our daily practice. A sudden increase in the CRP level in a febrile neutropenic patient triggered the start of new antibiotic treatment episode or broadening the spectrum of gram negative coverage. The meta-analysis of 13 studies including 1713 febrile episodes with serial CRP measurement showed that an increase in CRP levels were significantly associated with bacterial infection [17].

Carbapenems, glycopeptides, TZP, and colistin are restricted antibiotics that can be used only with the approval of an ID physician according to Turkish Ministry of Health regulation since 2003. A significant reduction in the consumption of carbapenems which was correlated with decreased carbapenem-resistant *Pseudomonas* spp. and *Acinetobacter* spp. infections was reported by a multicenter study from Turkey [18]. Neutropenic patients with cancer, particularly patients who received HSCT can experience severe infections and restriction of broad spectrum antibiotics can cause concern about delay in the effective treatment. This situation can motivate the ID physicians to use the broad spectrum antibiotics more easily if they are not familiar with infections in cancer and HSCT patients or if they do not constantly belong to the oncology/transplant team. Although the decision of starting or stopping these antibiotics were given by ID physicians who were being changed for each month at our center for years, decrease for the consumption of restricted antibiotics were significant after the assignment of a permanent ID physician at the HSCT center. American Society of Transplantation Infectious Diseases recommended "transplant infectious diseases" as a subspecialty and transplant ID physician was described as the most trusted consultant (but not the leader) as the transplant team whose primary responsibility is to recognize and treat the opportunistic infections as possible as early, but also should refine and limit the unnecessary use of antimicrobials [19, 20]. Long term involvement of ID physicians to the antimicrobial stewardship programmes in cancer centers with prospective audit and feedback to the other stakeholders of the multidisciplinary team resulted in the reduction of inappropriate use of carbapenem and vancomycin [21].

## CONCLUSION

Our analysis is limited with its retrospective nature such as absence of number of the patients with febrile neutropenia, rates of escalation/de-escalation of the primary antibacterial therapy, and number of the patients with community acquired infections admitted to HSCT, but the general demographic characteristics of the patients were similar when 2013 was compared with 2014. Even though rates of nosocomial infections and antibiotic resistance increased relatively in 2014, we were able to decrease the consumption not only carbapenems but also of glycopeptides and colistin. The sustainability of such intervention needs to be monitored continuously. Collaboration of the team members with face to face interactions can play an important role for long term success of antimicrobial stewardship intervention in cancer and transplant centers.

**Conflict of interest.** The authors have no conflicts of interest to disclose.

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