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Carbapenems Utilization Evaluation in Neutropenic Patients of a Teaching Hospital

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ABSTRACT

Background: Carbapenems is frequently prescribed for treatment or prophylaxis in neutropenic patients. It is cleared that antimicrobial misuse can cause poor patient outcomes, through raise of antibiotic resistance, increased adverse events, and prolonged length of hospital stay. We evaluated the rational use of Imipenem- Cilastatin and Meropenem for empirical antibacterial therapy in neutropenic patients based on Infectious Disease Society of America (IDSA) guideline.

Methods: Through this cross-sectional study, we assessed the appropriateness of administration of Carbapenems in neutropenic patients admitted in hematology–oncology and bone marrow transplant wards in Namazee hospital, Shiraz, Iran, from March 2012 to May 2013.

Results: Total of 90 patients was enrolled. Drug therapy duration was appropriate in 69.6% of Imipenem-Cilastatin and 75% of Meropenem groups. Sampling time of culture was appropriated in 59.1% of Imipenem-Cilastatin and 78.3% of Meropenem group, interval of drug administration was correct in 74.5% at initiation and 79.4% during therapy in Imipenem-Cilastatin group. For dosing these values were 74.5% and 72.2%, respectively. These values were evaluated in patients who received Meropenem too, interval was correct in 89.5% at initiation and 90.3% during therapy, dosing was correct in 12.3% both at initiation and during therapy.

Conclusion: These finding suggest that attention to correct dose, correct interval, renal dose adjustment, logical indication for administration of Carbapenem should be considered by health care system.

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Introduction

Febrile neutropenia is a typical problem in hematological malignancies and hematopoietic stem cell transplant (HSCT) (1, 2). Neutropenic patients are exposed to different types of strong bacterial and fungal infections, which can root systemic infections (3). Mortality rate is high in these types of patients hence prescribing of timely and appropriate empirical antibiotic therapy is unquestionably vital (4). Prophylaxis or treatment with antibiotics ought to be considered in these patients (5). On the other hand, Carbapenems are frequently prescribed for treatment or prophylaxis in neutropenic patients (6). Imipenem-Cilastatin and Meropenem are the most studied agents in this class (6). A primary concern of Carbapenems prescription is the emergence and spread of extended-spectrum beta-lactamase (ESBL)-producing bacteria and carbapenemase-producing bacteria (8). It is cleared that antimicrobial misuse can cause poor patient outcomes, through raise of antibiotic resistance, increased adverse events, and prolonged length of hospital stay (9). Furthermore, antibiotic-associated resistance is a major

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spending for institutions and is subsequent in a heavy worldwide economic burden (10, 11).

Definition of neutropenia is; ANC less than 500 cells/mcL or anticipated to drop to less than 500 cells/mcL within 48 hours (6). Severity and duration of neutropenia determines the risk of infection in neutropenic patients (6). Drug Utilization Evaluation (DUE) studies is an important aspect of gathering data for finding out the problems linking to the use of drugs that can assess the real process of prescription of drugs in addition to the results of the treatment (5). Unlike drugs such as vancomycin, therapeutic drug monitoring is currently not used to evaluate Carbapenems (12).

We directed this DUE study to evaluate the rational use of Imipenem- Cilastatin and Meropenem for empirical antibacterial therapy in neutropenic patients based on IDSA (Infectious Disease Society of America) guideline.

Methods

In a non-interventional, descriptive, cross-sectional study, we assessed the appropriateness of administration of Carbapenems (Meropenem and Imipenem) in neutropenic patients admitted in hematology–oncology and bone marrow transplant wards in Namazee hospital, which is linked to Shiraz University of Medical Sciences, from March 2012 to May 2013.

The patients who met the following criteria were included in this study:

1. Adulthood (≥18 years)
2. The patients who were neutropenic or developed neutropenia during the hospital course, who received one of the Carbapenems drugs including Imipenem or Meropenem

Patients who were released from treatment, or who died during the hospital course, were excluded from the study.

Neutropenia was defined as absolute neutrophil count (ANC) <1,500 cells/μL in adults (6). Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or

- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
- Urine volume <0.5 mL/kg/hour for six hours (7, 8).

To assess indicators of three types of Carbapenem drugs composed of Imipenem-Cilastatin and Meropenem, we designed a form containing information about clinical and demographic data, history of allergy to beta lactams, indication of prescription, the type of Carbapenems and its dosage, route, rate, and duration of administration, and their side effects. Also, we evaluated appropriate indication of administration, right dose (suitable according to guidelines), Compatibility with other drugs, interactions, adverse reactions, duration of infusion, initial dose, and further adjustment in cases who had increased in serum creatinine, appropriate dilution and stability (according to guidelines), cell blood count, serum creatinine, temperature and appropriate culture sampling. Also, we documented type of culture, organism and antibiogram (for positive culture).

The first step in this process was to collecting data such as; demographic, Drug History, medical history, Lab data, and invasive procedures was taken for patients, renal function (Serum Creatinine), vital signs, history of allergy to Betalactams. This data documented in a form for each patient.

For renal dose and interval adjustment of Carbapenems, the Cockcroft-Gault equation (6) was used, in initiation and during of administration. The patients categorized into two groups based to the risk of infection: high risk and low risk, this classification was done based to length of neutropenia (more than five days), or renal/ hepatic impairments. Duration of drug therapy was different in two groups.

In cases that establishment of causative pathogen or site of infection was done, the extent of therapy is based on the infection organism and site of infection and ought to stay at least until the ANC are 500/mcL or greater and increasing (2, 6). Generally, with effervescence (for at least 48 hours) and the patient hemodynamically stable or improving after initiation of therapy with no detectable etiology, empiric therapy had better to continue at least until the ANC are 500/mcL or greater and increasing (2, 6).

All the declared data were documented daily by a pharmacist in a form designed by a clinical pharmacist and infectious diseases specialist, for Carbapenems usage, administration, and monitoring. One log sheet was done for each patient. Then, collected data were revised by a clinical pharmacist and an infectious diseases specialist separately. According to Infectious Disease Society of America (IDSA) guideline printed in 2010, we evaluated the utilization of the declared Carbapenems in our wards.

We use the Multinational Association for Supportive Care in Cancer (MASCC) risk index, which is a validated tool for measuring the risk for neutropenic fever-related medical complications

We used SPSS version 18 for analysis of the data and to present the results descriptive statistics methods by excel software were used. Continuous variables were shown as mean ± standard deviation (SD), and categorical data were presented as percent and frequency.

Results

In this study 90 patients (73 in hematology-oncology ward and 17 in BMT ward) were enrolled, including 57 males and 33 females. Imipenem-Cilastatin was prescribed in 33 and Meropenem for 35 patients. In 22 patients Imipenem-Cilastatin changed to Meropenem due to shortage of drug in the study period. The patients' demographic data and are presented in Table 1. Indication of Carbapenems administration and types of underlying malignancy of patients and their frequency are shown in Tables 2 and 3 respectively.

Table1. Patients' demographics.

SEX n (%)	
Male	33 (37)
Female	57 (63)
Age (year)	
Mean (SD)	41.6 (16.01)
Weight (Kg)	
Mean (SD)	
	71.04 (13.64)
Height (cm)	
Mean (SD)	167.86 (9.44)
IBW (kg)	
Mean (SD)	62.4 (10.3)
Clearance Creatinine(mL/min) **Frequency (%)**	
Imipenem group	
6-20	2 (2.2)
21-40	3 (3.3)
41-70	11 (12.2)
>70	39 (43.3)
Meropenem Group	
10-25	1 (1.8)
26-50	4 (7)
>50	52 (91.2)

In Namazee hospital, Carbapenems administered intravenously, without combination with other drug and in conditions that stability was kept. Infusion time was correct (according to standards) in 40.9% and 65.2% of patients respectively in Imipenem-Cilastatin and Meropenem group..Minimum and maximum duration of Carbapenems therapy was 1 and 72 days respectively. Of course cases with duration less than 3 days were excluded from study. Mean of the duration of therapy was 17.25 days.

According to the guideline (2), duration of drug therapy was correct in 69.6% of Imipenem-Cilastatin and 75% of Meropenem groups. Initiation of Carbapenems administration in 88.6% of Imipenem-Cilastatin and 87% of Meropenem group was empirically. Prescription of Imipenem-Cilastatin and Meropenem in 90.9% and 84.4% of patients was indicated respectively. Our study showed that preparation of Imipenem-Cilastatin for injection was only correct in 9.1% cases. This value was 56.5% for Meropenem.

Basic ANC (ANC in first day of Carbapenems therapy) in 80.4% in Imipenem-Cilastatin and 75% in Meropenem group was less than 1500cell/mcL. At time of discharged from hospital 13% of Imipenem-Cilastatin and 6.8% of Meropenem group had ANC less than 500 cell/mcL.

77.3% of Imipenem-Cilastatin patients' group and 58.7% of Meropenem group were febrile (Temperature more than 38˚) in initiation of drug administration. These values decreased to 2.2% and zero, respectively.

Sampling time of culture was appropriated in 59.1% of Imipenem-Cilastatin and 78.3% of Meropenem group. But only in 12.2% of both groups' patient prescription of Carbapenems was done according to culture results.

Table2. Indication of Carbapenems Therapy

Indication of therapy	Frequency%
Neutropenia	38
Fever+ Neutropenia	32
Fever	4
pneumonia	8
Urinary Infection	2
Sinusitis	2
Skin infection	1
Septicemia	1
Diarrhea	1
Adverse Effect of Transplant	1

Table 3. Types of Underlying Diseases.

Disease	Frequency %
Acute Myeloblastic Leukemia	44
Acute Lymphoblastic Leukemia	20
Multiple Myeloblastic	6
Hodgkin Lymphoma	5
Non-Hodgkin Lymphoma	4
Osteosarcoma	2
Chronic Lymphoblastic Leukemia	2
Ovarian Cancer	1
Graft Versus Host Disease	1
Breast Cancer	1
Lung Cancer	1
Apelastic Anemia	1

We evaluated incidence of drug adverse reactions (ADR) and interactions in our study; ADR occurred in 37.8% of Imipenem-Cilastatin and 32.2% of Meropenem group. Most common ADR in both groups were nausea and vomiting.

Interaction with other drugs included (ganciclovir, valproic acid, cyclosporine) occurred in 2.2% of patients who received Imipenem-Cilastatin.

According to calculated creatinine clearance (Cockcroft and Gault formula) and guideline, interval of drug administration was correct in 74.5% at initiation and 79.4% during therapy in Imipenem-Cilastatin group. For dosing these values were 74.5% and 72.2%, respectively.

These values were evaluated in patients who received Meropenem too, interval was correct in 89.5% at initiation and 90.3% during therapy, dosing was correct in 12.3%

both at initiation and during therapy.

Discussion

In a recent meta-analysis by Horita et al., different antipseudomonal beta lactams were compared for successful treatment in febrile neutropenia. This meta-analysis recommends that Imipenem/Cilastatin, Meropenem and piperacillin Tazobactam may be reasonable first-choice medications for empiric therapy of febrile neutropenia (13). Although better outcome was reported in this meta-analysis with Carbapenems or piperacillin-betalactams, local susceptibility pattern should be considered.

One study showed that reduction of all-cause mortality by Carbapenems was more significant in compare with fourth generation of cephalosporin and anti-pseudomonas penicillin (14). Another study in Lebanon resulted that empirically administration of Imipenem-Cilastatin was suitable in 97.2% of patients (15). In 88.6% of Imipenem-Cilastatin and 87% of Meropenem groups, initiation of therapy was empirically, our study showed this. We concluded that 42.2% of patients were neutropenic and 35.6% of patients were febrile neutropenic at initiation of Carbapenems therapy. One study showed that 37% of patients received Imipenem empirically (16). This value was 80% for Meropenem in another study (17).We explant our results by this reasons; lack of attention to correct indication of administration, neglect of High and Low risk classification of patients, tendency to use wide-spectrum antibiotics, distrust to results of anti-bio gram, and weakness of sampling.

In our study initiation of Carbapenems therapy in 90.9% and 84.8% of Imipenem-Cilastatin and Meropenem patients' groups were correct, respectively. One study in Thailand showed that, initiation of Imipenem-Cilastatin was correct in 83% of patients (18). Different articles showed inappropriate empiric prescription of Carbapenems. Some reason could be considering to clear this point: insufficient knowledge about spectrum of antibiotics, mistake in prediction of Involved organisms, tendency to prescription of wide-spectrum or poly antibiotics, or prolonged duration of antibiotic therapy, antibiotic stewardship program could be have a role in improvement of rational administration knowledge accompany by role of pharmacist in setting of restriction for prescription of antibiotics (2, 19-21).

In a study that was performed in shariati hospitals' BMT ward in Tehran, Imipenem infusion time was corrected only in 15.6% of patients (22). Rapid infusion of Carbapenems can cause nausea but this adverse effect with Imipenem-Cilastatin was more common versus Meropenem (23). In our study infusion time in 40.9% of Imipenem-Cilastatin and 65.2% of Meropenem group was correct.

One study was done in Tehran showed duration of Imipenem-Cilastatin therapy was not correct in 51.6% of BMT patients (22). In another study this percent was 6 for septic patients (24). A recent systematic review and network meta-analysis research revealed that the Imipenem-Cilastatin treatment success rates were not significantly different from the majority of other common anti-biotical therapies in the febrile neutropenic patients. Besides, the researchers observed a lower Imipenem-Cilastatin treatment success rate in children (25).

In our study, duration of therapy in 69.6% of Imipenem-Cilastatin and 75% of Meropenem groups of patients was correct. Reasons of incorrectness were: drug disconnection when ANC was under normal range; patient was febrile or the time needed to eliminate specific microorganisms was not over (26, 27). In salehifar et al., study administration of Meropenem and duration of it were inappropriate in 34% and 28% of patients, respectively(26), On the other hand they concluded that dose and length of Imipenem therapy was right in 64 and 50 patients, respectively (27).We observed preparation errors in 91% and 43% of Meropenem and Imipenem-Cilastatin groups, respectively. Our opinion about this high rate of errors is that, pharmacists did not have a role in preparation.

ANC evaluated daily, 13% of Imipenem-Cilastatin and 6.8% of Meropenem group had ANC less than 500cell/mcL at the discharge day, although they should be discharged with normal ANC. We scrutinized the reason and observed that these patients had acceptable clinical condition and physicians prescribed oral antibiotics such as Cefixime, ciprofloxacin or Co-Amoxiclave for outpatient treatment (28, 29).

Patients evaluated daily for fever, although only non-febrile patients should be discharged (6), 2.2% of Imipenem-Cilastatin group were febrile at discharge day. Appropriated sampling was done in 59.1% of Imipenem-Cilastatin and 78.3% of Meropenem groups. According to guideline empiric antibiotic therapy should be consider in neutropenic febrile patients as long as the results of the cultures are specified (2, 22, 30). But our study showed that only in 12.2% of all of patients, culture results led to change antibiotics. This point can be interpreted as follows:

1) Negative cultures should not result in discontinuation of treatment, 2) non knowledge about therapeutic protocols, inappropriate sampling, failure to follow up culture results and lack of Lab cooperation.

Adverse drug effects were occurred in 37.8% of Imipenem-Cilastatin and 32.2% of Meropenem groups. Most common ADRs were nausea and vomiting. One study in Tehran, Iran showed nausea and vomiting in 57.8% of patients who received Imipenem-Cilastatin (22). Rapid infusion can augment nausea/vomiting of Carbapenems (23).

2.2% of Imipenem-Cilastatin group showed drug interaction with ganciclovir, valproate and cyclosporine. One study in 1999 showed convulsion resulted by interaction of Imipenem with ganciclovir (31).

We used Cockcroft and gault formula to calculate creatinine clearance in this study and based our Carbapenems dosage on creatinine clearance (19). Unfortunately, physicians did not pay much attention to the role of creatinine clearance changes in dosing regimens during treatment. Dose adjustment for Imipenem-Cilastatin group at initiation of therapy was performed for 74.5% of patients and in 72.7% dose adjustment based on creatinine clearance changes was done. Interval of Imipenem- Cilastatin in 74.5% of patients

at initiation and 79.4% of patient in duration of therapy were adjusted base on creatinine clearance.

Dose adjustment for Meropenem group at initiation and during of therapy was done base on creatinine clearance in 12.3% of patients. Interval adjustment at initiation and during of therapy was performed in 89.5% and 90.3% of Meropenem group respectively, according to creatinine clearance. Creatinine measured daily in our ward but our results suggested that, attention of physician to influence of creatinine value on dose and interval adjustment was not complete.

In 2013 one study suggested that, majority of febrile neutropenic patients do not received sufficient therapeutic Meropenem' dose (32).another study reported that 35.9% of patients who received Imipenem-Cilastatin need to dose readjustment (22). One study conducted in Qatar, compared two strategy of Meropenem dosing (1 g Q8 hour and 500 mg Q6hour) and founded no difference between them (7).

11.8% of Imipenem-Cilastatin and 10.7% of Meropenem group dead during the study. Another study was showed mortality in 15% of Imipenem-Cilastatin and 21% of Meropenem groups (14).

Our limitations in this study were: short time of study, Low number of patients, documentary deficiency and unpredictable exclusion of patients during the therapy.

In conclusion, an appropriate duration of therapy was observed in 69.6% of Imipenem-Cilastatin and 75% of Meropenem groups of patients; however, the preparation errors occurred in 91% and 43% of Meropenem and Imipenem-Cilastatin groups, respectively. These finding suggest that attention to correct dose, correct interval, renal dose adjustment, logical indication for administration of Carbapenem should be consider by health care system. Role of clinical pharmacist can be important to supervise administration of antibiotics; DUE studies must be performing routinely in hospitals.

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References

1. Alshukairi A, Alserehi H, El-Saed A, et al. A de-escalation protocol for febrile neutropenia cases and its impact on carbapenem resistance: A retrospective,quasi-experimental single-center study. J Infect Public Health 2016;9(4):443-51.

2. Freifeld AG, Bow EJ, Sepkowitz KA, 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(4):e56-93.

3. Glasmacher A, von Lilienfeld-Toal M, Schulte S, Hahn C, Schmidt-Wolf IG, Prentice A. An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients. Clin Microbiol Infect 2005;11(Suppl 5):17-23.

4. Irfan S, Idrees F, Mehraj V, Habib F, Adil S, Hasan R. Emergence of Carbapenem resistant Gram negative and vancomycin resistant Gram positive organisms in bacteremic isolates of febrile neutropenic patients: A descriptive study. BMC Infect Dis 2008;8(1):80.

5. Vazin A, Davarpanah MA, Ghalesoltani S. Antifungal agent utilization evaluation in hospitalized neutropenic cancer patients at a large teaching hospital. Drug Healthc Patient Saf 2015;7:97-102.

6. Alldredge BK, Corelli RL, Ernst M, Guglielmo BJ, Jacobson P, Kradjan WA. 10th ed. Koda-Kimble MA editor. Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs; 2013.

7. Wilby KJ, Nasr ZG, Elazzazy S, Lau TT, Hamad A. Review of Clinical Outcomes Associated with Two Meropenem Dosing Strategies. Drugs RD 2017; 17(1):73-78.

8. Issa N, Pedeboscq S, Le Quellec F, et al. Proper use of carbapenems: Role of the infectious disease specialist. Med Mal Infect 2016;46(1):10-3.

9. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf 2014;5(6):229-41.

10. Thabit AK, Crandon JL, Nicolau DP. Antimicrobial resistance: impact on clinical and economic outcomes and the need for new antimicrobials. Expert Opin Pharmacother 2015;16(2):159-77.

11. Smith R, Coast J. The true cost of antimicrobial resistance. BMJ 2013;346:f1493.

12. Arfa P, Karimi A, Rafiei Tabatabaei S, Fahimzad A, Armin S, Sistanizad M. A Prospective Study to Assess Vancomycin Serum Concentrations in Pediatric Patients with Current Dosing Guidelines. Iran J Pharm Res 2016;15(1):341-6.

13. Jing Y, Li J, Yuan L, et al. Piperacillin-tazobactam vs. imipenem-cilastatin as empirical therapy in hematopoietic stem cell transplantation recipients with febrile neutropenia. Clin Transplant 2016;30(3):263-9.

14. Edwards SJ, Clarke MJ, Wordsworth S, Emmas CE. Carbapenems versus other beta-lactams in treating severe infections in intensive care: a systematic review of randomised controlled trials. Eur J Clin Microbiol Infect Dis 2008;27(7):531-43.

15. Kabbara WK, Nawas GT, Ramadan WH. Evaluation of the appropriateness of imipenem/cilastatin prescription and dosing in a tertiary care hospital. Infect Drug Resist 2015;24(8):31-8.

16. Feldman C, White H, O'Grady J, Flitcroft A, Briggs A, Richards G. An open, randomised, multi-centre study comparing the safety and efficacy of sitafloxacin and imipenem/cilastatin in the intravenous treatment of hospitalised patients with pneumonia. Int J Antimicrob Agents 2001;17(3):177-88.

17. Punpanich W, Srisarang S, Prachantasen U. Therapeutic effectiveness of the

generic preparation of meropenem (Mapenem) in the treatment of moderate to severe infection in children. J Med Assoc Thai 2012;95(7):895-902.

18. Raveh D, Muallem-Zilcha E, Greenberg A, Wiener-Well Y, Schlesinger Y, Yinnon AM. Prospective drug utilization evaluation of three broad-spectrum antimicrobials: cefepime, piperacillin-tazobactam and meropenem. QJM 2006;99(6):397-406.

19. Cuthbertson BH, Thompson M, Sherry A, Wright MM, Bellingan GJ. Antibiotic-treated infections in intensive care patients in the UK. Anesthesia 2004;59(9):885-90.

20. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. N Engl J Med 1999;341(5):305-11.

21. Thuong M, Shortgen F, Zazempa V, Girou E, Soussy CJ, Brun-Buisson C. Appropriate use of restricted antimicrobial agents in hospitals: the importance of empirical therapy and assisted re-evaluation. J Antimicrob Chemother 2000;46(3):501-8.

22. Sakhaiyan E, Hadjibabaie M, Gholami K, et al. Drug Utilization Evaluation of Imipenem in Patients Undergoing Bone Marrow Transplantation. International Journal of Hematology-Oncology and Stem Cell Research 2009;3(2):10-13.

23. Mohr JF 3rd. Update on the efficacy and tolerability of meropenem in the treatment of serious bacterial infections. Clin Infect Dis 2008;47(suppl 1): S41-51.

24. Geddes A, Thaler M, Schonwald S, Härkönen M, Jacobs F, Nowotny I. Levofloxacin in the empirical treatment of patients with suspected bacteraemia/sepsis: comparison with imipenem/cilastatin in an open, randomized trial. J Antimicrob Chemother 1999;44(6):799-810.

25. 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(10):723-9.

26. Salehifar E, Shiva A, Moshayedi M, Kashi TS, Chabra A. Drug use evaluation of Meropenem at a tertiary care university hospital: A report from Northern Iran. J Res Pharm Pract 2015;4(4):222-5.

27. Shiva A, Salehifar E, Amini M, Ala S, Rafati MR, Ganji R. Drug Utilization Evaluation of Imipenem in an Educational Hospital in Mazandaran Province. Pharmaceutical Sciences 2014;20(1):12-17.

28. Schimpff SC. Empiric antibiotic therapy for granulocytopenic cancer patients. Am J Med 1986;80(5c):13-20.

29. Cortellaro M, Cofrancesco E, Pasargiklian I, et al. Ciprofloxacin for infection prophylaxis in granulocytopenic patients with acute leukemia. Haematologica 1990;75(6):541-5.

30. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016;27(S5):v111-v118.

31. Darville T. Imipenem and Meropenem. Semin Pediatr Infect Dis 1999;10(1):38-44.

32. Binder L, Schwörer H, Hoppe S, et al. Pharmacokinetics of meropenem in critically ill patients with severe infections. Ther Drug Monit 2013;35(1):63-70.