Utilization Evaluation of Antimicrobial Agents in Neutropenic Cancer Patients in a Teaching hospital: Urgent of Drug Utilization Evaluation Studies

Hadi Hamishehkar[1*], Elnaz Zoghi[2], Hadi Chavoushi[3], Simin Ozar Mashayekhi[4], Parina Asgharian[5], Taher Entezari-Maleki[6], Haleh Rezaee[7]

[1] Drug Applied Research Center, Department of Clinical Pharmacy (Pharmacotherapy), Tabriz University of Medical Sciences, Tabriz, Iran.

[2] Iranian Evidence Based Medicine Center of Excellence, Tabriz University of Medical Sciences, Tabriz, Iran.

[3] Hematology and oncology Research Center, Faculty of medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

[4] The Liver and Gastrointestinal Research Center, Tabriz University of Medical sciences, Tabriz, Iran.

[5] Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

[6] Department of Clinical Pharmacy (Pharmacotherapy), Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

[7] Infectious Diseases and Tropical Medicine Research Center, Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

ARTICLE INFO

ABSTRACT

Background: More than 80% of patients with hematologic malignancies will develop fever during more than one chemotherapy cycle combined with neutropenia. We aim to evaluate empiric antibiotic strategies in Febrile Neutropenic (FN) cancer patients.

Methods: This is a concurrent study performed in the "Shahid Ghazi" teaching hospital, hematology-oncology center of Tabriz, Iran during the period of December 2011 to September 2012. During this period, patients with FN were evaluated in view of antibiotics utilization based on Infectious Disease Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) instructions.

Results: Seventy patients had a total of 91 episodes of FN in the duration of this study. Among them 63 (90%) patients were the cases of acute leukemia. For 88 (96.7 %) patients, imipenem was used as the initial empirical antibiotic regimen. It was changed to piperacillin/tazobactam in 8 (8.8%) of them without indication. Cultures didn't obtain before the initiation of empirical therapy in 19 (20.9%) episodes. Empiric vancomycin didn't discontinue after 3 days even if it was not warranted in 23 episodes. In 16 cases vancomycin was switched to teicoplanin. The fluconazole dosages generally given to patients were all suboptimal. Adjusting the dosages of vancomycin or imipenem was not done correctly in 13 (14.29%) episodes.

Conclusion: The results of this study showed that choosing antimicrobial agents and their dosing for prophylaxis and treatment of FN patients and discharge antimicrobial planning of FN patients do not follow the evaluated guidelines. Drug Usage Evaluation studies need to be done regularly in such a center.

J Pharm Care 2014; 2 (1): 3-9.

* *Corresponding Author*: Dr Hadi Hamishehkar
Address: Department of Clinical Pharmacy (Pharmacotherapy) Faculty of Pharmacy,Tabriz University of Medical Sciences, Daneshgah St. Tabriz-Iran,
P.O. Box: 51664-14766.Tel: +984113344798/Fax:+984113341315
E-mail: hamishehkar@tbzmed.ac.ir

Introduction

Many patients suffer from hematology/oncology disorders have had their lives lengthened through therapeutic advances in chemotherapy, despite such advances, infectious complication is an ongoing struggle (1).

Neutropenia as the main dose limiting toxicities of chemotherapy drugs, lead to prolonged hospitalization, reducing chemotherapy agents dose and delay in the treatment of curable cancers (2). Neutropenia is explained as an absolute neutrophil count (ANC) of 500 cells/ microL or an ANC that is suspected to reduce to, 500 cells/mm³ during the next 48 h (2, 3).

Hospital care accounts for almost 40% to 50% of the total costs of cancer care (4). Therefore a febrile neutropenia (FN) episode is a medical emergency and practitioners must be aware of how to control it immediately (5).

Antimicrobial agents are administered with larger frequency and for a higher number of indications (prophylaxis, empiric therapy, targeted therapy, maintenance therapy) in cancer patients than in most other patient population. This has led to the raise in the emergence of resistant pathogens (6). Antimicrobial resistance is a global issue that needs urgent reaction. One of the effective measures to promote correct use of antimicrobials and delay antimicrobial resistance is the antimicrobial stewardship program (7). Therefore balancing the need for enough antibiotic use, management of infections and the prevention of antimicrobials overuse continue to be a major challenge. Few studies have addressed the problem of antibiotic usage in FN patients (6).

Medication errors can happen at all stage of therapeutic process consisting prophylaxis, empiric antibiotic administration, modification in empiric strategy through addition of another antibiotic or antifungal agent and dosage calculation (8). Emphasis on rational use of medications in the FN group could attenuate the risk and enhance the quality of care (5).

We have conducted a prospective study in febrile neutropenic patients to evaluate antibiotics utilization and determining the prevalence, and the type of antibiotic-related prescribing errors.

Patients and Methods

This study has been designed based on Infectious Disease Society of America (IDSA), 2010 update by the Infectious Diseases Society of America, and National Comprehensive Cancer Network (NCCN) instructions in the absence of nationally defined guideline. Adult patients with both solid tumors and hematological cancer who undergone antineoplastic chemotherapy were eligible for this study if they had episode of neutropenia and fever.

Neutropenic patients were selected according its definition explained above. Fever is described as a single oral temperature measurement of >38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained over a 1 hour period (2). Since the data about blood temperature were recorded by the use of axillaries temperatures in this unit, 0.5 degree were added to them (9).

This is a prospective descriptive study conducted in the "Shahid Ghazi hospital" teaching hospital during the period from December 2011 to September 2012. This hospital is the only hematology-oncology center of the north-west of Iran in Tabriz city.

Relevant information from each patient's chart was obtained. The data were recorded in a predesigned data collection form. It includes demographic characteristics of the patient (e.g. age, sex, weight...), underlying malignancy and the type and the date of recently given chemotherapy regimen. Also Medical history and co morbidities such as diabetes mellitus and hypertension were recorded. Some subjective data on medical problems were obtained by patient interview.

For the purpose of Drug Utilization Evaluation (DUE) detailed information about antibacterial prophylaxis against infection, initial regimen, adjuvant glycopeptides (vancomycin or teicoplanin) and any additional antibacterial were recorded. Antifungal and antivirus agents prescribed to the patients also were assessed. In addition the date of starting and stopping of antibiotic regiment and dosages of all antimicrobial agents were recorded and dose adjustments were checked based on renal function.

Day-to-day amounts of ANC, fever, blood pressure and serum creatinin concentration and some important laboratory diagnostic data were collected using patient's chart.

Hemodynamic instability, abdominal pain, nausea, diarrhea, neurologic or mental status changes and a new pulmonary infiltrate, all have effects on process of treatment so were considered as criteria. Any improvements of patient status were also used to assign the rationality of practitioners' decisions.

Microbiological culture/sensitivity testing from blood, urine, stool or any exact colonization site was recorded.

Duration of fever and neutropenia and duration of treatment were investigated at the end of treatment course.

Whenever data extraction and interpretation was unclear, health professionals (physicians, residents or nurses) were consulted to arrive at a consensus. The management strategies were evaluated according to current guidelines and descriptive analyses of data were performed using SPSS software (version, 16).

Results
Demographics

Seventy patients had a total of 91 episodes of fever and neutropenia. Among them, 63 patients (90%) were the cases of acute leukemia (Table 1). Nine cases were primarily outpatient. Among them 3 cases were

Table 1. Demographic characteristics of patients.

Male sex, n (%)	57 (62.6%)
Age, years	34.8 ± 15.7 (12-86)
Duration of neutropenia, days	11 ± 10.2
Duration of fever, days	10 ± 10.3
Duration of Antibiotic therapy, days	14 ± 10.4
Underlying malignancy disease, N=91 (%)	
AML	52 (57.1)
ALL	33 (36.3)
Lymphoma	2 (2.2)
Other types	4 (4.4)

Data are presented as mean ± SD
AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia

Table 2. Antimicrobial regimen prescribed as prophylaxis and initial empirical therapy.

Regimen	Number of episodes (%)
Prophylactic antimicrobial agents	
None	15 (16.5)
Cotrimoxazole	71 (78)
Ciprofloxacin	1 (1.1)
Cotrimoxazole + Fluconazole	2 (2.2)
Ciprofloxacin + Fluconazole + Cotrimoxazole	1 (1.1)
Cotrimoxazole + Ciprofloxacin	1 (1.1)
Initial antibiotic treatment	
Imipenem	88 (96.7)
Ciprofloxacin	2 (2.2)
Meropenem	1 (1.1)

hospitalized to get their chemotherapy but it wasn't started because the diagnosis of fever and neutropenia related to their last session of chemotherapy.

The Multinational Association for Supportive Care in Cancer (MASCC) Risk Index was used to identify high-risk patients (score < 21 points) regarding some factors in febrile neutropenia (including burden of illness, dehydration, clinical setting at onset of fever, age, tumor type, respiratory failure, hypotension). The score was developed to select patients for therapeutic strategies that could potentially be effective. In this study all the cases were high risk because most of them were the case of hematological malignancy, inpatient at onset of fever and burden of illness was severe.

Culture results

Cultures weren't acquired before the initiation of empirical therapy in 19 episodes (20.9%). The results of obtaining cultures were missed since they weren't attached to the patients chart in 10 episodes (Figure 1). The 13 positive cultures comprised of 9 cases of blood stream infection, 2 cases of urinary tract infection (UTI), 1 case with yeast from stool culture. One patient had both blood stream infection and UTI.

All gram-negative species were E.coli and 5 episodes of 6 Gram-positive cultures were Staphylococcus aureus. Cotrimoxazole susceptibility test result was reported for 8 episodes in which 7 episodes consisting 4 E.coli and 3 Staphylococcus aureus were resistant. All of them were received cotrimoxazole as prophylaxis regimen. Antibiogram assay of ampicillin was evaluated for 5 episodes of positive E.coli and all of them were resistant. Two episodes of resistance were also reported about ceftizoxime, cephalotin and cephalexin in which one case of resistance to cephalotin and cephalexin was E.coli and

others were staphylococcus aureus.

Antiviral therapy

Of the 17 cases who got antiviral therapy, 3 cases (17.64%) were due to seropositivity (about herpes simplex virus) and the others (n=14; 82.35%) were based on clinical observations.

Prophylaxis and initial antibiotic regimen

For the majority (n=75; 82.4 %) of episodes, cotrimoxazole was utilized as a part of prophylactic antibiotic regimen. The results are shown in Table 2. Fluoroquinolone prophylaxis was used only in 3 patients whose their malignancy was recently diagnosed and it was their first period of chemotherapy. These 3 cases were all febrile prior to their treatment.

In 4 episodes, empirical therapy was carried out with delay and error was occurred since it should be begun in the first day of FN but the treatment has been started after the mean of 2±0.8 days. Monotherapy with imipenem was the initial empirical antibiotic regimen in 88 episodes (96.7%) (Table 2).

Imipenem was changed to piperacillin-tazobactam in 8 episodes (8.8%) after the mean days of 10.87 (±3.2) persistent fever. Ciprofloxacin used in 2 episodes has been changed to imipenem.

Addition of antibiotics and antifungal agents

Thirty nine patients received vancomycin in its exact indication. Empiric vancomycin was continued after 3 days even if it was not necessary anymore in 23 episodes. In 17 cases, vancomycin was switched to teicoplanin, which in 9 episodes it has been administered because of renal impairment. In the other 8 episodes persistent fever led to this modification (Table 3).

Table 3. Administration of anti Gram-positive agents.

Indication for Vancomycin	Number of episodes (%)
Truly treatment with Vancomycin	39 (42.85)
Indicated but was not prescribed on time	1 (1.09)
Continued after 3 days without indication	23 (25.3)
Vancomycin changed to Teicoplanin	16 (17.58)

Figure 1. Frequency of microbial cultures performed for FN patients in the duration of neutropenia.

Metronidazole was prescribed for 32 episodes (35.2%), which in all of them it was indicated. Two patients (2.2%) needed to be prescribed because of diarrhea and abdominal pain but they didn't receive metronidazole.

Addition of other antibiotics has done in 9 episodes which was injudicious in 3 of them included prescription of clindamycin and amoxicillin/clavulonate. Nitrofurantoin was added to regimen of one case because culture result was positive. In the other 5 cases fluoroquinolones were added to the initial regimen correctly for management of complications (e.g., hypotension and pneumonia).

Antifungal agent was not prescribed in 11 FN episodes (12%) after 5 to 7 days with consistent fever. In 2 episodes receiving fluconazole prophylaxis, although it should be switched to an antimold, fluconazole was continued as empirical regimen inappropriately.

Dosing

Overally, there was a mistake in antimicrobial dosing in 39% of all cases. The fluconazole dosages generally given to patients were all suboptimal (200 mg instead of 400 mg). Acyclovir dosing errors occurs in 6 patients. Adjusting the dosages of vancomycin or imipenem were not done correctly in 13 episodes (14.29%) (Figure 2).

Outcome and discharge planning

Clinicians decided to discharge the patients after fever abated and when ANC recovered above 500 cells/microL. Despite such carefully decisions some prescriptions were ordered to 14 episodes as their follow up consisting ciprofloxacin, coamoxiclave, cefixime, cephalexin, cotrimoxazole, clindamycin or fluconazole but there is not any indication for keeping on antibiotic for them.

Response to initial empirical therapy occurred in 25 episodes (27%) after 24-48 h without need to add a glycopeptides. Among FN patients evaluated in this study 10 of them were died.

Discussion

No previously published studies have examined the practice of managing FN in Iran oncology units. Although any institutionalized protocols was not used for antimicrobial prophylaxis in this hospital but the data shows that the practitioners don't refer to use fluoroquinolone prophylaxis. It may be because of concerning about side effects and antimicrobial resistance. However based upon the available data, fluoroquinolone prophylaxis should be used for patients who are at high risk of profound prolonged neutropenia (ANC ≤ 100 cells/microL for >7 days) but although at institutions that consider fluoroquinolone prophylaxis, systematic monitoring of the incidence of fluoroquinolone resistance among gram-negative bacilli is advised (2). The question of when to initiate and discontinue fluoroquinolone chemoprophylaxis has not been systematically studied. Many clinicians begin prophylaxis treatment with the first day of cytotoxic therapy or the day following administration of the last dose of chemotherapy, and they stop at the termination of the neutropenic period or, for those patients who develop fever, at the initiation of empirical antibiotic therapy (2).
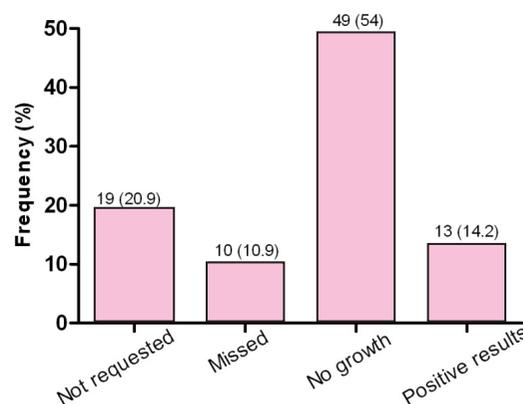
The delay between onset of fever and initiation of antibiotic therapy which occurred in 4 episodes was related to the method of fever measurement. The difference between oral and axillary fever was not considered so error occurred to diagnosis of fever initiation. A total of 82.4% of episodes have been received the drug cotrimoxazole as prophylaxis regimen. Although according to NCCN Guidelines prophylaxis for P.jirovecii is necessary to ALL cancers, two published 5-year and 10-year studies show that the prevalence of infection in other hematological malignancies such as AML and lymphomas is also likely so P.jirovecii prophylaxis in these cases seems to be reasonable too (10, 11). The duration of pneumosistis prophylaxis is throughout anti-leukemic therapy which properly regarded in this hospital (3).

Infection is the main treatment-related cause of mortality in cancer patients (12). By the way, in this study, only in 13 (14.28%) episodes responsible pathogens were recognized. Recently it was found that rapid and appropriate diagnostic way other than cultures to facilitate
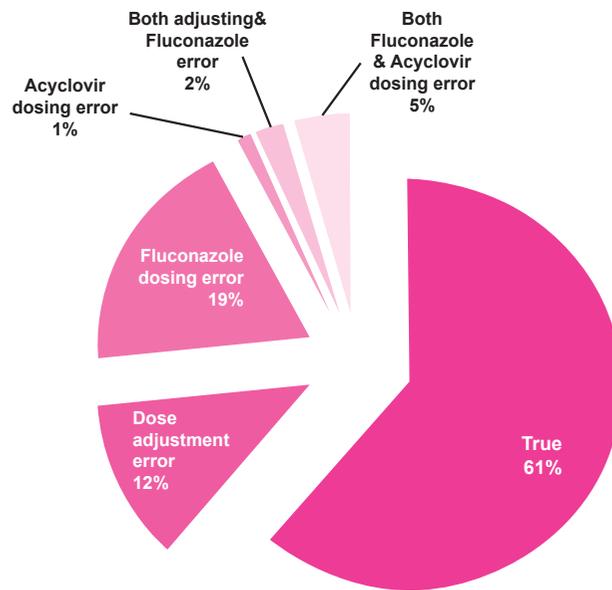
Figure 2. Frequency and types of dosing errors, if the dose ordered was an overdose or underdose; an overall error rate of 39% was found.

specific therapy of febrile neutropenia is urgently needed (12). Since the mid-1990s, the proportion of Gram-negative infections has decreased with a proportional increase in Gram-positive infections (13). The results of this study show an equal incidence of gram-positive and gram -negative pathogens among the positive culture results

Empirical antibiotic monotherapy in high risk patients include the prescribing of an antipseudomonal beta lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam (2, 3) . As it was pointed, in 96.7% of cases imipenem was used as empirical therapy. Changing the regimen to piperacillin-tazobactam in 8 episodes demonstrates clinicians not only are unconfident to culture results but also they are uncertain about bacterial sensitivity to imipenem anymore. In a systematic literature review of 15 years randomized controlled trials of imipenem for Pseudomonas clinical success and microbiologic eradication rates were directionally lower for imipenem than for comparators (14). Several interventions have been proposed to help control the complication. One of these is a process of planned antibiotic restriction, introduced through cycling drug selection based on local surveillance (15). As another solution, many institutions have elected to reserve the carbapenems for patients who have failed to respond to prior empiric therapy, have a history of infections with pathogens resistant to third- and fourth-generation cephalosporins, are clinically unstable, or have need for expanded anaerobic coverage (16).

If any gram-positive active agent is appended to the initial regimen for clinical reasons, it should be discontinued after 2 or 3 days if susceptible bacteria were not obtained from the patient (2). Nonetheless, we noticed that it was not regarded in 23 (25.3%) episodes. It confirms again the hypothesis of clinicians' hesitancy about laboratory data and their uncertainty about patient outcome without gram-positive coverage.

Whereas vancomycin was able to restrict staphylococcal, streptococcal, and enterococal infections 2 decades ago, the average resistance rate among enterococal species in the United States in 1999 has risen to 18% and is higher (30%) among patients with malignancy (17). Teicoplanin and vancomycin have similar efficacy and the same spectrum of activity (18). Recently systematic review noted a lower risk of nephrotoxicity with teicoplanin than with vancomycin (18, 19). Due to high price and lack of insurance coverage for teicoplanin in Iran, vancomycin is more cost effective. Therefore in 8 episodes without renal impairment prescribing teicoplanin is considered unacceptable. Other antimicrobials (aminoglycosides and/or fluoroquinolones) may be added to the initial regimen for control of some situations (e.g., hypotension, pneumonia or lung infiltration) or if antimicrobial resistance is expected or proven (2). The carbapenems are a unique class of antibiotics with broad-spectrum activity against numerous Gram-positive and Gram-negative bacteria, including anaerobes (16). Thus adding some other antibiotics for instance clindamycin and coamoxiclave is not required.

Antifungal agent was not prescribed in 11 FN episodes after 5 to 7 days with consistent fever, a finding which doesn't conform to the guidelines.The Infectious Diseases Society of America recommends considering an antifungal agent after 4 to 7 days in high-risk patients (i.e., neutropenic patients who are suspected to have a total duration of neutropenic of >7 days) who have persistent or recurrent fever (2). In patients who have not been receiving antifungal prophylaxis, Candida spp. is the most likely cause of invasive fungal disease thus in patients receiving fluconazole prophylaxis, invasive mold infections or fluconazole-resistant Candida spp. are the most feasible (2, 3). So in the only 2 episodes receiving fluconazole prophylaxis, amphotericin B or voriconazole for empiric antifungal therapy was favorable and error occurred about drug choice.

Fluconazole dosing in FN patients is mentioned 400 mg/day for duration of neutropenia (3). Remarkably Inappropriate (low) dosing of fluconazole has been observed in this study. The suboptimal use of fluconazole may lead to increasing resistance and decreasing efficacy (20). When dose adjustment is not done carefully, inappropriate (high) dosing is demonstrated. This point is crucial because imipenem increased seizure risk and thrombocytopenia have been reported in patients with significant renal dysfunction (21). About vancomycin the usual risk factors of neurotoxicity and nephrotoxicity have been illustrated by pre-existing renal impairment and concomitant nephrotoxic medications (22). Acyclovir dosing was suboptimal in 6 cases. The correct acyclovir dosages for mucocutaneous herpes simplex virus (HSV) infectin are as below:

Intravenous (I.V.): Immunocompromised: Treatment: 5 mg/kg/dose every 8 hours for 7 days (23); dosing for up to 14 days also reported

Oral (unlabeled use): Immunocompromised: 400 mg 5 times/day for 7 days (23).

The usual oral dosing which used in this center was 400 mg 3 times/day. I.V. administration was only used for one patient which was sub optimal according to patient's weight.

In conclusion the results of this study showed that choosing antimicrobial agents and their dosing for prophylaxis and treatment of FN patients and discharge antimicrobial planning of FN patients do not follow the evaluated guidelines completely. The lack of DUE studies and updated treatment instructions in this population may lead to the improper administration of antimicrobials in centers with high rate of antimicrobial utilization. Monitoring antimicrobial prescription, including the quantity and patterns of use and feedbacking results to clinicians accelerates treatment procedure.

Acknowledgements

References

1. Bow EJ. Management of the febrile neutropenic cancer patient: lessons from 40 years of study. Clin Microbiol Infect 2005;11 (Suppl. 5):24-9.

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-e93.

3. NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections.National Comprehensive Cancer Network (NCCN).V.2.2011. Available from: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf.

4. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006 ;106(10):2258-66.

5. Akova M, Alp S. Management of febrile neutropenia in the era of bacterial resistance. Ther Adv Infect Dis 2013;1(1):37-43.

6. Wade JC. Current issues in the treatment of resistant bloodstream infections. Oncology 2000;14(8 Suppl 6):35-9.

7. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44(2):159-77.

8. Stolar MH. Conceptual framework for drug usage review, medical audit and other patient care review procedures. Am J Hosp Pharm 1977;34(2):139-45.

9. Alpern ER HF. Fever. In: Fleisher GR L, S HF, editors. Textbook of pediatric emergency medicine. 5 ed. Philadelphia: Lippincott Williams & Wilkins 2006. p. 295-306.

10. Pagano L, Fianchi L, Mele L, et al. Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. Br J Haematol 2002;117(2):379-86.

11. Roblot F, Le Moal G, Godet C, et al. Pneumocystis carinii pneumonia in patients with hematologic malignancies: a descriptive study. J Infect 2003;47(1):19-27.

12. Von Lilienfeld-Toal M, Lehmann LE, Raadts AD, et al. Utility of a commercially available multiplex real-time PCR assay to detect bacterial and fungal pathogens in febrile neutropenia. J Clin Microbiol 2009;47(8):2405-10.

13. Coullioud D, Van Der Auwera P, Viot M, Lasset C. Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. Support Care Cancer 1993;1(1):34-46.

14. Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. Imipenem resistance of Pseudomonas in pneumonia: a systematic literature review. BMC Pulm Med 2010;10:45.

15. Masterton RG. Antibiotic cycling: more than it might seem? J Antimicrob Chemother 2005;55(1):1-5.

16. Drew RH. Prevention and Treatment of Infections in Neutropenic Cancer Patients. In: Koda-Kimble MA, editor. Applied therapeutics : the clinical use of drugs. 10 ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

17. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial Bloodstream Infections in United States Hospitals: A Three-Year Analysis. Clin Infect Dis 1999;29(2):239-44.

18. Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DD, Silva E. Teicoplanin versus vancomycin for proven or suspected infection. Cochrane Database Syst Rev 2010;16(6).

19. Vazquez L, Encinas MP, Morin LS, et al. Randomized prospective study

comparing cost-effectiveness of teicoplanin and vancomycin as second-line empiric therapy for infection in neutropenic patients. Haematologica 1999;84(3):231-6.

20. Garey KW, Pai MP, Suda KJ, et al. Inadequacy of fluconazole dosing in patients with candidemia based on Infectious Diseases Society of America (IDSA) guidelines. Pharmacoepidemiol Drug Saf 2007;16(8):919-27.

21. Leo R, Ballow C. Seizure activity associated with imipenem use: clinical case reports and review of the literature. Annal Pharmacother 1991;25(4):351-4.

22. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66(1):82-98.

23. Leflore S, Anderson PL, Fletcher CV. A risk-benefit evaluation of aciclovir for the treatment and prophylaxis of herpes simplex virus infections. Drug Saf 2000;23(2):131-42.