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Drug Utilization Evaluation of Agents Administered for Prevention and Treatment of Cancer-Related Infections

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ABSTRACT

Background: Due to the critical role of antibiotics and increasing trend of resistance in developing countries, comprehensive methods of antibiotic use is necessary to limit the threat of resistant microorganisms. In this study we compare antibiotics consumption by Defined Daily Dose (DDD) per 100 bed-days in Shahid Ghazi hospitals during three months in Tabriz, Iran.

Methods: This is a retrospective study, which enrolled patients with malignancy who admitted to Shahid Ghazi hospital from January till March 2016. From all, 58 patients diagnosed with malignancy and received antibiotics for prophylaxis and/or treatment. For the purpose of Drug Utilization Evaluation (DUE) all antibiotics, antifungals and antiviruses consumption for any reason (prophylaxis, empiric therapy, targeted therapy) were recorded. Data on administered medications such as indication, duration, and dose were compared according to the guidelines of the NCCN 2.2016. The accuracy of antibiotics consumption was assessing by NCCN (2.2016) guideline. Anatomical Therapeutic Chemical (ATC) code J01 was explained as defined daily doses per 100 bed-days (DDD/100) according to the ATC/DDD classification. The amount of consumption was assessed with DDD per 100 bed-days in three months.

Results: from 56 patients, 46 of them had hematologic malignancy and 10 of them had solid tumors. The indication of antibiotics and antifungal prophylaxis were wrong in 19.6% of indications. The prophylaxis dosage of antibiotics, antifungal, antiviral and PCP were wrong in 8.8%, 41.7%, 80% and 50%, respectively. The prophylaxis duration of antibiotics, antifungal, antiviral and PCP were wrong in 69.4%, 61.2%, 80% and 100% respectively. The dose adjustment of antibiotics with GFR and renal status of patients, in 8 of 9 patients (88.88%) who received meropenem, and in 9 of 23 patients (39.13%) who received imipenem, were not applicable according standard guidelines. The total consumption of systemic antibiotics in Ghazi Hospital during 3 months was 5091 (Table 7(.

From all patients 75% of them received antibiotics according to the ATC/DDD classification System.

Conclusion: Specific strategies should be employed in infection control development and engage rational antibiotic utilization in order to reduce future resistant strains and increase anti-microbial efficacy.

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Introduction

Antibiotic resistance infections are currently a vital and serious phenomenon in communities that widespread across the world (1). Bacterial resistance causes many problems in treatment of hospitalized patients (2). Resistant organisms are responsible for many types of nosocomial infections, moreover are associated with the length of hospital stay and mortality (3). The crisis of antibiotic resistance is in result of overuse, misuse and inappropriate prescription in hospitals (4). studies indicated that incorrect prescription with not applicable indication, dose, and duration were seen in 30 of 50 % of cases (4, 5). In 1966 Reiman and Ambola studied about the use of antibiotics on cancer patients in the United States, the results show that most antibiotics are misused (6). Antimicrobials have played an undeniable role in curing many serious infectious diseases since their discovery and have increased the life expectancy among the people of the world (7, 8). But misdiagnosis of antibiotics, despite being beneficial, can lead to serious complications or long-term illness (9). Bacteria, fungi and viruses are the main microorganism associated with causing infection. Intensive mold infectious caused by some fungal species are related with life threatening infections in patients with neutropenia (10). During past 3 decade viruses have a main roles in the multistage progress of neoplasms, moreover these agents are associated with 15% to 20% of cancer infections (11, 12). Side effects of chemotherapy drugs such as nausea and vomiting, fever and neutropenia, and other symptoms have led to overuse of drugs in this patients. One of the most common side effect of chemotherapy drugs in cancer patients is neutropenia, which itself can causes infection and reduces life expectancy. However the use of appropriate antibiotics to prevent infections is reasonable (13). Moreover, appropriate management of other side effect of chemotherapy such as nausea and vomiting is also important (14).

ATC classification system is the most broadly used classification system for expression of drug consumption(15). The ATC system is harmonized by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. In the ATC system, drugs are divided into different groups according to their act and/or their chemical properties and therapeutic effect. Therefore, each specific drug is categorized to five different levels and is determined at least one ATC code. DDD is statistical measure that designed by the WHO to compare drug consumption average maintenance dose per day for the drug's main indication in adults. Also For different drug formulations (i.e., parenteral versus oral), other DDDs are determined (16). On the other hand, drug consumption is expressed with rate. Common units for antibiotic utilization rate can be defined by DDD per 100 bed-days in hospitals(15).

Lack of information about the pattern of antibiotic use necessitates further studies and documented information in this area. In this study, we evaluate the administration of antibiotics, antifungals, and antivirals as prophylaxis and treatment in patients who admitted to hematology and oncology ward. In addition, the pattern of physicians adherence to the NCCN reference guideline (2.2016) was assessed in this study (17).

Methods

This retrospective cross-sectional observational study was conducted in Hematology and Oncology Center of Tabriz University of Medical Sciences. The study was preformed from January to March (2016) in Tabriz, Iran. The study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences. Patients participated in the study with informed consent and their medical information remained confidential.

Fifty-eight patients with definitive diagnosis of malignancy and received antibiotics for prophylaxis and/or treatment were included in the study. Patients with Immune Thrombocytopenic Purpura (ITP), Hemolytic Anemia, Aplastic Anemia, Thrombotic thrombocytopenic purpura (TTP), Megaloblastic anemia were excluded from the study. Based on the pre-designed data collection form, demographic information including: age, sex and weight, as well as type of disease, hospitalization duration, and laboratory findings were collected. Moreover, all antibiotics, antifungals and antiviruses consumption for any reason (prophylaxis, empiric therapy, targeted therapy) were recorded for the purpose of Drug Utilization Evaluation. Data on administered medications such as indication, duration, and dose were compared according to the guidelines of the NCCN 2.2016. In addition, the onset timing and stopping date of antibiotic regimen of all antimicrobial agents were obtained. Dose adjustments were assessed according on renal and liver function.

The ATC code J01 expressed as defined daily doses per 100 bed-days (DDD/100) according to the ATC/DDD classification. The equation of DDD amount is mentioned in equation 1. For Calculation of DDD per 100 bed-days (DDD/100), total amount of each drug dispensed based on DDD is divided into bed day and multiply by 100 (equation 2). It should be mentioned that, bed day is calculated by multiplying the total number of patients in each period by number of days in that period (equation 2) (15).

Total use of DDD for each drug =(usual dose)/(ATC/DDD) ×Quantity dispensed Eq. [1]

DDD per 100 bed−days =(Total od DDDs for each drug)/(bed day)×100Eq. [2]

In patients with cancer and with low risk of infection, prophylaxis of antimicrobial agents is not required. However, in patients with a moderate to high risk of bacterial infection, prophylaxis with fluoroquinolones should be initiated (18). Initiation of prophylaxis is not routinely recommended in all patients with neutropenia. Azoles, amphotericin B, and echinocandins are antifungal drugs found in the fungal infection prevention protocol in cancer patients. In addition, acyclovir, famciclovir, and valaciclovir are antiviral drugs that are prescribed as a prophylaxis in patients at moderate to high risk of viral infections. In Patients with a high risk of infection with pneumocystis jirovecii, prophylaxis of trimethoprim / sulfamethoxazole are highly effective (19).

Cancer patients with low risk of infection and the Patients with no history of kidney or hepatic failure and as well as patients who are 21≤ score in the MASCC rating system, are at low risk for neutropenia related infection. In these patients the medications that were considered are in oral form and included ciprofoxacin or levofoxacin and co-amoxiclav. Cancer patients with high risk of infection and patients with history of kidney or hepatic failure, patients who received alemtuzumab and as well as patients who are 21≥ score in the MASCC rating system, are at high risk for neutropenic infection. Treatment in patients at high risk of uncomplicated febrile neutropenia is intravenous monotherapy and included with cefepime, or imipenem/cilastatin, or piperacillin/tazobactam, or meropenem and/orceftazidime(20, 21). It's noted that, in patients at high risk for neutropenic complicated fever, effective drugs against multiple antibiotics resistant pathogens should be added to treatment protocol.

For data classification and analysis, version 21 of SPSS software was used. Quantitative data were expressed as mean ± SD and qualitative data as percentage. Chi-squared test was used to compare qualitative variables between the two groups. If the default is not determined, Fisher exact test was used. If the conversion is inadequate or insufficient, the Mann-Whitney U test was used for abnormal variables.

Results

Related information was collected from 56 eligible cancer patients who were admitted to Shahid Ghazi Hospital. Out of 56 patients, 46 patients with hematologic malignancy and 10 patients with solid tumors were admitted. Demographic characteristics, underlying malignancy, type of cancer, and patient renal function are shown in Table 1.

Table 1. Information on sex, type of hematology malignancy and tumor, patients' fate and renal glomerular filtration rate.

Factor		frequency(%)*
Gender	Male	36(64.3)
	Female	20(37.7)
Hematologic malignancy	AML	23(50)
	ALL	11(23.9)
	CML	2(4.3)
	CLL	3(6.3)
	Lymphoma	5(10.8)
	MM	2(4.3)
Solid tumor	Sarcoma	3(30)
	GI cancer	1(10)
	Endometrial cancer	2(20)
	Adenocarcinoma	4(40)
Fate	Expired	5(8.9)
	Lived	51(91.1)
glomerular filtration rate	Less than 30	2(3.6)
	Less than 50	3(5.4)
	More than 50	51(91.1)

AML: acute myeloid leukemia,ALL: Acute lymphoblastic leukemia, CML: Chronic myelogenous leukemia,CLL: Chronic lymphocytic leukemia, MM: Multiple myeloma.

The results based on the evaluation of the prophylactic indication showed that antibacterial, antifungal and PCP antibiotic prophylaxis in 45 (80.4%) of patients were administrated according standard guidelines. Furthermore, the standard indication for antiviral prophylactic administration was not applicable in all of 56 patients (100%). Evaluation of antimicrobial prophylactic dose and duration indicated the prophylactic dose of antibiotic agents (ciprofloxacin) in 8.8%, antifungal (fluconazole) in 41.7%, PCP (Co-trimoxazole) in 50% and antiviral (acyclovir) in 80% of cases were not appropriable with the standard guidelines. In addition, the duration of prophylactic antibiotics (ciprofloxacin) in 69.4% of cases, antifungal agents (fluconazole) in 61.2%, PCP (Co-trimoxazole) in 80% and antiviral agents (acyclovir) in 100% cases were not applicable according to standard guidelines. 42 of 56 (75%) patients received antibiotics to treat infection. Out of 42 patients who received antibiotics to treat the infection, imipenem was the most used antibiotic (38.1%), followed by meropenem (14.3%), co-amoxicalve (14.3%), ceftriaxone (11.9%). Moreover, carbapenem with vancomycin (9.5%), ciprofloxacin (4.5%), clindamycin (2.4%), metronidazole with carbapenem (2.4%) and clindamycin with ciprofloxacin

(2.4%), were detected, respectively. Antimicrobial drugs and the time of addition of ciprofloxacin, vancomycin and antifungals showed that the treatment protocol was not applicable to the protocol in 87.5%, 66.1% and 78.6% of patients, respectively. Results of the time of adding of drugs for infection treatment is shown in Table 2.

Table 2. The onset timing of prophylaxis and its relationship to the need for treatment.

Time of prophylaxis	Treatment Number(%)*	No treatment Number(%)*
Neutropenia	0	1(2.4)
Chemotherapy	1(2.4)	3(21.4)
1 day before chemotherapy	6(14.3)	3(21.4)
2 days before chemotherapy	3(21.4)	2(14.3)
3 days before chemotherapy	3(7.1)	1(7.1)
More than 3 days before chemotherapy	5(11.9)	2(14.3)
After chemotherapy	5(11.9)	2(14.3)
No prophylaxis	19(45.2)	0

The dosage of antibiotics and antifungals for the dosage evaluation treatment of fever and neutropenia is shown in Table 3. Out of 56 patients, 16 patients received antifungal drug; 2 patients received nystatin, 1 patient received simultaneously nystatin and fluconazole, and 13 patients received carbapenem with metronidazole. Doses of antibiotics and antifungals to evaluate the treatment dose for fever and neutropenia are shown in Table 3.

Table 3. Evaluation of dosage treatment.

Antibiotics	Correct dose	Number(%)*
Meropenem	Yes	1(8.3)
	No	11(91.7)
Imipenem	Yes	14(58.4)
	No	10(41.7)
Vancomycin	Yes	18(94.7)
	No	1(5.3)
Ciprofloxacin	Yes	7(100)
	No	0(0)
Clindamycin	Yes	2(66.6)
	No	1(33.3)
Metronidazole	Yes	12(92.3)
	No	1(7.7)
Amphotericin B	Yes	4(100)
	No	0
Caspofungin	Yes	9(100)
	No	0

*Categorical variables are presented in percent (%)

Out of 56 patients, 16 patients received antifungal medication. 2 patients received nystatin, 1 patient received nystatin and fluconazole simultaneously and 13 patients received carbapenem with metronidazole. The relationship between the indications, doses and duration of prophylaxis of antibiotics, antifungals and antivirals with the type of cancer, the patient's fate, the number of hospitalizations and evaluation for treatment of fever and neutropenia are shown in Table 4, 5 and 6, respectively.

Table 4. The relationship between the indications for prophylaxis of antibiotics, antifungals and antivirals with the type of cancer, the patient's fate, the number of hospitalizations and whether or not to receiving antibiotics for treatment

Indication prophylaxis		Antibiotic		p value	Antifungal		p value	Antiviral		p value	PCP		p value
		yes	no		yes	no		yes	no		yes	no	
Type	Solid tumor	2(20)	8(80)	1	8(80)	2(20)	1	10(100)	0		10(100)	0	0.183
	Hematologic malignancy	37(80.4)	9(19.6)		37(80.4)	9(19.6)		46(100)	0		35(76.1)	11(23.9)	
Fate	Lived	9(17.6)	42(82.4)	0.251	40(78.4)	11(21.6)	0.571	51(100)	0		41(80.4)	10(19.6)	1
	Expired	2(40)	3(60)		5(100)	0		5(100)	0		4 (80)	1(20)	
Cycle	Cycle1	23(82.1)	5(17.9)	0.676	25(89.3)	3(10.7)	0.262	28(100)	0		22(78.6)	6(21.4)	0.767
	Cycle 2	11(84.6)	2(15.4)		9(69.2)	4(30.8)		13(100)	0		10(76.9)	3(23.1)	
	Cycle 3	6(66.7)	3(33.3)		6(66.7)	3(33.3)		9(100)	0		9(88.9)	1(11.1)	
	Cycle 4	2(100)	0		2(100)	0		2(100)	0		1(50)	1(50)	
	Cycle 5	1(50)	1(50)		1(50)	1(50)		2(100)	0		2(100)	0	
	Cycle 6	2(100)	0		45(80.4)	11(19.6)		2(100)	0		2(100)	0	
Treatment	Treatment	9(21.4)	33(78.6)	0.711	36(85.7)	6(14.3)	0.119	42(100)	0		34(81)	8(19)	1
	No treatment	12(85.7)	2(14.3)		9(64.3)	5(35.7)		14(100)	0		11(78.6)	3(21.4)	

Table 5. The relationship between the prophylactic dose of antibiotics, antifungals and antivirals with the type of cancer, the patient's fate, the number of hospitalizations and whether or not to receiving antibiotics for treatment.

Dose prophylaxis		Antibiotic		p value	Antifungal		p value	Antiviral		p value	PCP		p value
		no	yes		no	yes		no	yes		no	yes	
Type	Solid tumor	1(50)	1(50)	0.003	0	2(100)	0.004	0	0	1	0	0	1
	Hematologic malignancy	30(93.7)	2(6.3)		15(44.2)	19(55.8)		1(20)	4(80)		1(50)	1(50)	
Fate	Lived	27(93.2)	2(6.8)	0.056	13(42)	18(58)	0.241	0	4(100)	0.123	1(50)	1(50)	1
	Expired	4(80)	1(20)		2(40)	3(60)		1(100)	0		0	0	
Cycle	Cycle1	1(5.8)	16(94.2)	0.432	7(46.7)	8(53.3)	0.304	1(25)	3(75)	0.940	0	0	0.095
	Cycle 2	1(20)	4(80)		2(25)	6(75)		0	1(100)		0	1(100)	
	Cycle 3	1(14.2)	6(85.8)		3(42.9)	4(57.1)		0	0		0	0	
	Cycle 4	0	1(100)		2(100)	0		0	0		0	0	
	Cycle 5	0	2(100)		0	2(100)		0	0		0	0	
	Cycle 6	3(8.3)	31(91.2)		1(50)	1(50)		0	0		1(100)	0	
Treatment	Treatment	20(91)	2(9)	0.058	10(43.5)	13(56.5)	0.029	1(25)	3(75)	1	1(100)	0	0.441
	No treatment	11(91.7)	1(8.3)		5(38.5)	8(61.5)		0	1(100)		0	1(100)	

Table 6. The relationship between the prophylactic duration of antibiotics, antifungals and antivirals with the type of cancer, the patient's fate, the number of hospitalizations and whether or not to receiving antibiotics for treatment.

Duration prophylaxis		Antibiotic		p value	Antifungal		p value	Antiviral		P value	PCP		p value
		no	yes		no	yes		no	yes		no	yes	
Type	Solid tumor	0	2(100)	0.007	0	2(100)	0.006	0	0	1	0	2(100)	1
	Hematologic malignancy	11(32.3)	23(67.7)		14(41.1)	20(58.9)		1(20)	4(80)		0	0	
Fate	Lived	11(35.4)	20(64.5)	0.043	12(38.7)	19(61.3)	0.199	0	4(100)	0.123	0	2(100)	1
	Expired	0	5(100)		2(40)	3(60)		1(100)	0		0	0	
Cycle	Cycle1	7(38.8)	11(61.2)	0.268	9(56.2)	7(43.8)	0.228	1(25)	3(75)	0.940	0	0	0.095
	Cycle 2	2(40)	3(60)		3(42.8)	4(57.2)		0	1(100)		0	1(100)	
	Cycle 3	1(14.2)	6(85.8)		1(14.2)	6(85.8)		0	0		0	0	
	Cycle 4	1(50)	1(50)		1(50)	1(50)		0	0		0	0	
	Cycle 5	0	2(100)		0	2(100)		0	0		0	0	
	Cycle 6	0	2(100)		0	2(100)		0	0		0	1(100)	
Treatment	Treatment	5(21.7)	18(78.3)	0.006	8(34.7)	15(65.3)	0.176	1(25)	3(75)	1	0	1(100)	0.441
	No treatment	6(46.1)	7(53.9)		6(46.1)	7(53.9)		0	1(100)		0	1(100)	

We assessed the onset of prophylaxis and its effect on the need for treatment. The results showed that out of 56 patients, 42 patients received treatment regimen. 19 out of 42 patients were treated without prophylaxis. In addition, 17 of 42 patients (40.7%) received prophylactic regimen before chemotherapy and 5 of 44 patients (11.9%) received prophylactic regimen after chemotherapy. Evaluation of the dose adjustment of antibiotics with GFR and renal status of patients showed that, 8 of 9 patients (88.88%) who received meropenem, 9 of 23 patients (39.13%) who received imipenem, were not applicable according standard guidelines. The total consumption of systemic antibiotics in Ghazi Hospital during 3 months was 5091 (Table 7).

Table 7. Total antibiotic consumption based on ATC / DDD classification system.

Class	Available anti-bacterial	Use (DDD/100 BD)	%
Penicillins with extended spectrum(J01CA)	Amoxicillin	0.024	0.5
Carbapenems(J01DH)	Imipenem	0.14	3.1
	Meropenem	0.06	1.3
Cephalosporins(J01DA)	Ceftriaxone	0.04	0.9
Macrolides(J01FA)	Azithromycin	0.04	0.9
	Clindamycin	0.23	5.2
Quinolones (J01M)	Ciprofloxacin	Oral(0.71)	16
		Parenteral(0.05)	1.1
	Levofloxacin	0.005	0.1
Imidazole derivatives(J01XD)	Metronidazole	0.21	4.7
Glycopeptides	Vancomycin	0.65	14.7
Azoles(J02AC)	Fluconazole	0.21	4.7
Echinocandins (J02AX)	Caspofungin	2.32	52
Macrolides (G01AA03)	Amphotericin B	0.004	0.09
Macrolides (J01AA)	Nystatin	0.03	0.6

*Categorical variables are presented in percent (%)

Discussion

Antibiotics are one of the widely used drugs in hematology and oncology wards in hospital. There are logical reasons to use the appropriate antibiotics with correct dosage and duration to prevent infection and bacterial resistance. The present study was conducted to compare antibiotics consumption by Defined Daily Dose per 100 bed-days and administration of antimicrobial drugs according to the NCCN 2.2016 guidelines in Shahid Ghazi Educational and Medical Hematology and Oncology Hospital.

Antimicrobial prophylaxis guidelines recommend physicians to initiate agents based on the standard indications as well as onset of administration, the appropriate dose, and the standard duration of prophylaxis. Studies on antibiotic prophylaxis in patients at risk of infection showed that the prophylaxis administration in these patients reduced the incidence of bacterial infection (22).

Fluoroquinolone can entirely reduce the mortality rate in neutropenic patients with moderate to high risk group as well as the incidence of fever and bacteremia (23, 24). In addition, a study on antibiotic prophylaxis for bacterial infections in a febrile neutropenic patients following chemotherapy showed a reduction in all mortality parameters in the ciprofloxacin prophylaxis receiving group (25). Fluoroquinolone can completely reduce mortality in neutropenic patients with moderate to high risk groups as well as the incidence of fever and bacteria (23, 24). In addition, a study on antibiotic prophylaxis for bacterial infections in neutropenic febrile patients following chemotherapy showed a diminution in all mortality parameters in the ciprofloxacin prophylaxis group (25).

According to NCCN guidelines, prophylaxis for P.jirovecii is essential for patients with ALL cancers, and some studies have reported that prevalence of infection in other hematological malignancies such as AML and Lymphomahas has decreased (26, 27).

According to the result of analyzing our data; antibacterial,

antifungal and PCP agent prophylactic indications were prescribed in majority of patients (80.4%) according to the routine guidelines. However, antivirals prophylactic administrations were not applicable in all of patients who received this agent. In this study, we found that prophylactic indications were not applicable in more than half of inpatients who were expired. In addition, in patients who received antibiotic for treatment, prophylactic indications significantly (78%) did not confirm according the standard guidelines.

We found that the dosage and duration of antibiotic and antifungal prophylactic agents in patients with cancer were often not applicable according the guidelines. These results show a direct relation between adherence to the principles of prophylaxis as an indication, dose and duration with the onset of the patient's infection and necessitates the need for antibiotics for treatment.

The most important treatment-related cause of mortality in patients with cancer is infection (28). An infection symptoms and signs or infection without present of fever or hypothermia in a neutropenic patient should always raise the suspicion of infection and uses of antibiotic empiric treatment. The progression of the infection in a neutropenic patient with cancer is very rapid and the type of primary infection is difficult to diagnose. Patients with cancer may become infected due to receiving of chemotherapy during hospitalization (29).

According to the treatment guidelines as well as prophylaxis, some principles as an appropriate dosage, duration of treatment, and time of addition of antimicrobial agents to the protocol of treatment should be adjusted appropriately to eliminate the infections. The DDD number is a suitable quantitative unit to express antimicrobial use and criteria for level of antimicrobial utilization.

The results of our study indicated that of all patients, 75% of them received antibiotics. In high risk patients for infection and the patients with a 21≥ score in the MASCC rating system, empirical antibiotic monotherapy with antipseudomonal beta lactam agent such as cefepime, imipenem/cilastatin, piperacillin/tazobactam, meropenem and ceftazidime should be initiated (17, 18). Imipenem was the most common used antibiotic (38.1%) in Shahid Gazi Hospital for the treatment of infection. However, in nearly half of patients (41.7%) the dose of imipenem for was inappropriately administered to treat the infection. In our findings, the dose of meropenem was inappropriate in 91.7% of patients. In a study by Al-Hadithi and et al., meropenem was administrated empirically in 96% of patients. In these patients the dosage and indication of meropenem for infection treatment were prescribed according to the guidelines in 87% and 49% of patients, respectively (30).

In a study by Kabbara and et al., about evaluation of the appropriateness of imipenem/cilastatin administration and dosing in a tertiary care hospital, the indication use of these drugs empirically was appropriate in 97.2% of the cases. In addition, in 33% of patients the prescribed dose of antibiotics was not confirmed according to the guidelines (31). In another study in Thailand by Raveh and et al., the initiation of Imipenem-Cilastatin was applicable according to the guidelines in 83% of patients (32). However, in our study the treatment with vancomycin, the dose of antibiotic was prescribed appropriately in 94.7% of patients. In a study at the Shiraz Medical Center on the evaluation of vancomycin consumption, the results were similar to our analysis, and they reported that vancomycin was prescribed with appropriate dose for the treatment of infection in 68.3% of cases (33).

In a study by Bahador and et al., duration of imipenem-cilastatin and meropenem administration as an empirical therapy was applicable in 69.6% and 75% of patients, respectively. Moreover, indications for initiation of carbapenems therapy in 90.9% of patients were appropriately administrated (34). In a study at Shariati Hospital in Tehran, in 51.6% of Bone marrow transplant patients, the duration of treatment with Imipenem-Cilastatin was not confirmed according guidelines (35).

Ciprofloxacin and fluconazole were the most widely used antibiotic and antifungal in our center according to the ATC / DDD Classification system. Selecting appropriate antibiotic dose to treat infection in patients with cancer, as well as dose adjustment with GFR status and renal function, is essential, more than ever in renal failure patients (36).

In our study, dose adjustment of imipenem with renal function was not confirmed in 39% of patients. In a study by Sakhaian and et al., about drug utilization evaluation of imipenem in patients undergoing bone marrow transplantation, as in our study in 35.9% of patients with renal failure or low weight, dose adjustment not taken at the time (35).

It's important to be watchful with dose adjustment and be careful about inappropriate dosing administration. As it was pointed, in patients with severe renal dysfunction, imipenem may increase the risk of thrombocytopenia and seizure (37). We determined that the total use of systemic antibiotics in Ghazi Hospital during the three months was low and it was 4.419 DDD / 100 BD. In study of Ghaffary and et al., about measurement and comparison of antibiotic use, the total use of systemic antibiotics in 5 sub specialties and general hospitals in different fields and multi type inpatients was 87.49 DDD/100BD (38). In addition, the results of another study in Serbia showed that the total use of systemic antibiotics was 224.85 and 263.54, respectively (39). It should be noted that patients who admitted to non-oncological wards did not receive

antibiotics routinely and the reason for the low rate of ATC / DDD-based drug consumption in our study is that we calculated the DDD only for patients who hospitalized at the hematological ward.

In conclusion, data derived from the evaluation of the pattern of administration and utilization of antibiotics, antifungals and antivirals drugs according to NCCN 2.2016 guideline for inpatients with cancer from January till April (three months) of 2016 in shahid ghazi hospital show that prophylactic indication, dose and duration by antimicrobial agents and treatment doses for infection significantly were administered inappropriately. Therefore, the overall review and new attitude should be institutionalized by policy-makers for standardized using of antimicrobial agents in treatment of infection in hospitals. Specific strategies should be employed in infection control development and engage rational antibiotic utilization in order to reduce future resistant strains and increase antimicrobial efficacy. In order to minimize inappropriate prescribing, as well as to prevent drug resistance and reduce hospital costs in Hematologic and Oncology wards, it's very important to use related international standard guidelines. Holding retraining courses for physicians as well as the presence of trained nurses in wards is necessary. The presence of clinical pharmacists in hospitals to regularly check the dose of drugs, setting alarms for re-adjusting the dose of antibiotics in cases of long-term use, seems reasonable to reduce the probability of errors in prescribing of antibiotic. Moreover, infection control, more attention to receiving and sending culture samples before initiating antibiotics is necessary to achieve our goals. It's clear that antimicrobial utilization evaluation and compare the patterns of consumption of these agents and their accommodation according standard guidelines help us to achieve our goals about reducing drug resistance and highly effective antibiotic administration.

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