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RESEARCH ARTICLE

EVALUATION OF CARBAPENEM USE AMONG PATIENTS AT INTENSIVE CARE UNIT (ICU) IN SANA'A, YEMEN

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Abstract

Objective: Drug Utilization Evaluation (DUE) studies are designed to evaluate and improve the rational use of medications. In this study, DUE has focused on drugs used in high risk patients such as critically ill cases. Carbapenems are beta-lactam type antibiotics with broad-spectrum of activity which cover gram-positive, gram-negative and anaerobic bacteria. The heavy use of carbapenems (imipenem or meropenm) could increase the risk of multi-drug resistant (MDR) pathogens. This study was a prospective and cross sectional study performed at intensive care unit (ICU) of Al-Matwakel hospital in Sana'a, Yemen.
Methods: The study was conducted from September 2018 to March 2019. All of the patients were on imipenem or meropenem as an empiric treatment or based upon microbiology culture results included in the study. Total of 80 patients at ICU were evaluated. **Results:** The results of the study showed that empiric therapy was in most cases (91.25%; *p<0.001*). In addition; about 36.3% of the patients required dosage adjustment according to glomerular filtration rate (GFR) stages. Also according to GFR calculation, 43.8% of the patients were in stage 3. In the present study, the frequency of therapeutic duplication of ceftriaxone with carbapenem was reported in 38 patients. The major drug-drug interactions were observed with tramadol-imipenem, tramadol-meropenem, and amlodipine-simvastatin.
Conclusion: The result of the study showed that empiric therapy was unjustified in most cases (91.25%). In addition, about 36.3% of the patients required dosage adjustment according to GFR stages. According to GFR calculation, 43.8% of the patients were in stage 3. In the present study, the frequency of therapeutic duplication and drug-drug interactions were observed.
Keywords: Carbapenem, empirical, GFR, imipenem, MDR, meropenem.

INTRODUCTION

One of the most important elements in patient care process is to evaluate the appropriateness of medication use. Medications review studies are aimed to evaluate and improve the rational use of drugs. They have mostly focused on drugs with higher cost, higher dispensing, relatively narrow therapeutic margin and also broad spectrum antibiotics. They also focus on medications prescribed in specialized populations such as elderly, critically ill, post-surgical and cancer patients[1]. Carbapenem (imipenem⁄cilastatin and meropenem) drugs are beta-lactam type antibiotics with a broad spectrum of activity and coverage of Gram-positive and Gram-negative aerobic and anaerobic bacteria. Imipenem⁄cilastatin and meropenem use have increased as a result of high resistant rates to other antibiotics[2]. Like other broad spectrum antibiotics, carbapenems are prescribed as a part of empiric therapy in most serious hospitalised infections. Imipenem is a semisynthetic carbapenem co-administrated with cilastatin, to prevent renal metabolism of imipenem by dehydropeptidase I (DHP I). In contrast, this co-administration with the renal dehydropeptidase inhibitor, cilastatin is not necessary with meropenem, because this agent is not hydrolyzed by DHP I[1]. The incidence of imipenem⁄cilastatin and meropenem resistance is increasing. One of the reasons could be the heavy use of these broad spectrum antibiotics in hospitalized patients including Intensive Care Units (ICUs)[3]. Improving the ICU environment involves education of critical care staff regarding the rational use of these drugs[1]. According to a study conducted in Sana'a, Yemen by Alyahawi *et al.*,[4] the resistant rate of meropenem based on culture results was seen in 25.3% of all collected isolates. In this

study, utilization of these antibiotics in critically ill patients was reviewed.

METHODS

The study was performed in ICU at a private hospital in Sana'a, Yemen. All the patients on carbapenem drugs from September, 2018 to March, 2019 were included. A total of 80 folders of the patients on carbapenem drugs were collected from ICU at the mentioned study period. The study protocol was approved by the institutional ethical committee. The data was analyzed in order to identify dosage adjustment according GFR stages, carbapenem selection according to culture results or empirical therapy, major and moderate drug-drug interactions and antibiotic used in combination with carbapenem. Statistical analysis was done by SPSS software version 21.0 by using Pearson's Chi-square test. Categorical variables were expressed as percentages. *p*-value of less than 0.05 was considered significant.

RESULTS

Total of 80 patients at ICU were evaluated. The results of the study showed that 78.8% of the study sample was men and 21.3% were women. Also 43.8 of the study sample were aged >= 60 years old. In the present study, 80% of the patients were on meropenem and 20% of total patients on imipenem drug. According to the glomerular filtration rate (GFR) classification, 43.8% of patients had chronic kidney diseases (CKD) stage 3.

Table 1: Distribution of the study variables.

Variable		Frequency	%
Gender	M	63	78.8
	F	17	21.3
Age group	0-19	4	5
	20-39	21	26.3
	40-59	20	25
	>=60	35	43.8
Imipenem		16	20
Meropenem		64	80
CKD Stage	1	12	15.0
	2	11	13.8
	3	35	43.8
	4	19	23.8
	5	3	3.8

From the study findings, 36 of patients with chest infection (45%) were onimipenem/cilastatinor meropenem, followed by patients with sepsis (25%).
According to glomerular filiation rate, there was 36.3% of carbapenem drugs (imipenem/cilastatin or meropenem) were needed dosage adjustment according to GFR stages. In addition, one carbapenem drug is not recommended by evidence used for patient. However, 8.8% of carbapenem drugs were used in low doses (Table 3).Table 4 showed the frequency of moderate drug-drug interactions in the present study. According to the drugs.com and Medscape, the frequency of moderate drug-drug interactions between all the patients' drugs was observed in 11 types. Detailed comments were reported in Table 4.
The frequency of major drug-drug interactions was demonstrated in Table 5. According to the drugs.com and Medscape, the frequency of major drug-drug interactions between all the patients' drugs was observed in three patients. Detailed major drug-drug interactions were reported in Table 5. In this study, there were 91.3% of patients on carbapenem drugs as empirical therapy ($P < 0.001$) However, 8.8% of patients used carbapenem drugs according to culture results. Figure 1 showed the percentage of antibiotics used before carbapenem administration for the study sample. Carbapenem drugs were administered in 75% of the patients as the first line. In contrast, 25% of patients used other antibiotics before carbapenem administration.

Table 2: Distribution of Carbapenem drugs used according to diagnosis.

Variable		Carbapenem used		Total
		Imipenem/ cilastatin	Meropenem	
Diagnosis	Brain Infection	1	2	3
	Chest Infection	9	27	36 (45%)
	CSF Infection	0	1	1
	Head Infection	0	1	1
	Meningitis	1	6	7
	Osteomyelitis	0	5	5
	SBP	0	1	1
	Sepsis	2	18	20 (25%)
	UTI	3	3	6
Total		16	64	80

The review of the patients' drugs showed different drugs related problems. According to the study findings, the frequency of therapeutics duplication with carbapenem drugs was in 41 (51.3%) of patients. Moreover, the therapeutic duplication of ceftriaxone with carbapenem drugs was in 38(92.7%) of these patients. In addition, one patient with urinary tract infection (UTI) was on moxifloxacin drug (less effective for UTI). Carbapenem drugs have a broad spectrum of activity, so most other antibiotics are unnecessary as combination to carbapenem (Table 7).

Table 3: Dosage adjustment according to GFR stages.

Variable	Frequency	%
Need dosage adjustment	29	36.3
Not need dosage adjustment	43	53.8
Low dose	7	8.8
Not recommended	1	1.3
Total	80	100.0

DISCUSSION

Applying standard treatment guidelines with training and supervision can guide physicians in the appropriate use of carbapenem drugs in hospital. Generally, most physicians use carbapenem drugs empirically for patients admitted to the ICU without the identification the exact infection. They may be to think that all patients admitted to ICU have a severe infection[5]. Continuous drugs education by therapeutic committee and regular drug utilization evaluation programs could help in the rational medication use.

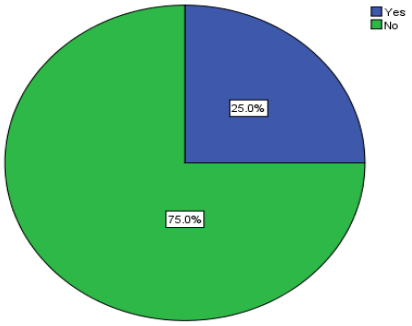

Figure 1: Antibiotics used before carbapenem.

The various clinical conditions and severity of infection for patient in ICU need the use of drugs from different classes[6].

Table 4: Moderate Drug-Drug Interaction.

Type of drug-drug interaction	Frequency
Aspirin-Clopidogrel	3
Aspirin-Heparin	1
Azithromycin-Simvastatin	1
Captopril-Heparin	1
Ceftriaxone-Warfarin	1
Metronidazole-Phenytoin	2
Phenytoin-Insulin	1
Phenytoin-Nifedipine	1

The results of this study revealed that the majority of patients (43.8%) received carbapenem drugs were equal or above 60 years old. Similarly, a study conducted for evaluation of meropenem utilization in intensive care unit in Sudan by Sanhoury *et al.*,[5] which found majority of patients, above 60 years old, received meropenem drug. In the current study, 91.3% of carbapenem drugs were prescribed without culture results; which means that these drugs were prescribed depending on physician' experience or on the severity of infection, but not according to isolated bacteria. This was not in agreement with a study conducted to evaluate the use of carbapenem in a French University hospital by Jary *et al.*, which found 60% of meropenem was prescribed empirically[7].

Table 5: Major drug-drug interactions.

Type of Drug-drug interaction	Frequency
Amlodipine-Simvastatin	1
Tramadol-Imipenem	1
Tramadol-Meropenem	1

The irrational utilization of broad-spectrum antibiotics such as carbapenem can lead to the development of various resistant strains of bacteria. These contribute significantly to increase in the costs of health care and morbidity and mortality of patients[8]. So, monitoring and evaluation of antimicrobial agents are one of the significant recommended strategies to prevent, control resistance, and to improve the rational use of these drugs[5]. The high prevalence of resistance in intensive care units (ICUs) is a key factor to increase the severity of the patient's illness, prolonged hospital stays, and the overuse of broad spectrum antibiotics. The selection of antimicrobial drugs for hospitalised infections is often driven by the patterns of hospital resistance and bacterial susceptibility surveillance. This can assist in clinical decisions regarding empirical antimicrobial therapy at each hospital[9].

Table 6: Carbapenem selection according to culture or empirical therapy.

Variable	Frequency	%
Empirical Therapy	73	91.3
According to culture results	7	8.8
Total	80	100.0

The request for the overuse of antibiotics such as carbapenem drugs as well as noncompliance with infectious disease guidelines both contribute to the increase of bacterial resistance. In United States, 20% of resistance rates were reported to imipenem/ cilastatin. It was regularly used for infection of high suspected *P. aeruginosa*[10]. The choice of appropriate dose of imipenem/cilastatin should be based on the location and severity of the infection, the susceptibility of the isolated pathogen(s), and the renal function of the patient. Adult patients with impaired renal function, as defined by creatinine clearance (Cr Cl)<70ml /min/1.73 m^2, require dosageadjustment[11]. According to results of current study, there was 36.3% of carbapenems (imipenem/cilastatin and meropenem) were required dosage adjustment according to GFR stages. This is similar to the results by a study conducted in Iran by Shiva *et al.*,[12], which found that the dosage of imipenem was inappropriate in 36% of patients, and the dosage adjustment (when needed) was either not done or done inappropriately in 64.3% of patients. Shiva *et al.*, also evaluated the utilization of imipenem/ cilastatin in an educational hospital in Iran and found that there was a high empirical prescription of imipenem/cilastatin without considering culture and antimicrobial susceptibility results, and they observed there was a lack of attention to dosage adjustments in patients with renal insufficiency[12]. Furthermore, in another study conducted by Sakhaiyan *et al.*, reported that the dosage adjustment of imipenem/cilastatin was not prescribed appropriately at their institution, and the researchers concluded that there was a need to more education for the health care professionals regarding the carbapenem dosage adjustment and their adjustment depends on the weight and the renal function of the patient[13]. Disorders of central nervous system (CNS) and kidney insufficiency had high risk

factors for seizure occurrence. Therefore, the patients who received imipenem/cilastatin at higher than recommended doses had an increased risk of seizures, particularly in patients with kidney insufficiency[14]. Some studies found that the high consumption of carbapenems drugs was attributed for the prevalence of carbapenem-resistant Gram-negative bacteria[15]. In March 2017, the National Health and Family Planning Commission (NHFPC) launched a special stewardship in clinical use of carbapenems[16]. According to the evaluation of drug-drug interactions in the present study, the major drug-drug interactions between all the patients' drugs were observed in three patients (Table 5). Co-administration with amlodipine may significantly increase the plasma concentrations of simvastatin and its active metabolite, simvastatin acid, and potentiate the risk of statin-induced myopathy. The proposed mechanism is amlodipine inhibition of simvastatin metabolism via intestinal and hepatic CYP450 3A4. Limit simvastatin dose to no more than 20 mg/day when used concurrently. In addition, the risk of seizures may be increased during co administration of tramadol with any substance that can reduce the seizure threshold, such as carbapenems (imipenem/cilastatin or meropenem). These agents are often individually epileptogenic and may have additive effects when combined[17,18]. The evaluation of patients' drugs showed the frequency of therapeutics duplication with carbapenem drugs (beta-lactam antibiotics) was in 41 (51.3%) of patients. In addition, the therapeutic duplication of ceftriaxone with carbapenem drugs was seen in 38 (92.7%) of these patients. Furthermore, carbapenem drugs have a broad spectrum of activity, so most other antibiotics are unnecessary as combination to carbapenem drugs such as levofloxacin and moxifloxacin. In this study, one patient with urinary tract infection (UTI) was on moxifloxacin drug. Not all fluoroquinolones can be used for urinary tract infections based on their pharmacokinetic profiles. Moxifloxacin achieve considerably lower concentrations in the urine than other quinolones and are not approved for this indication[19].

Table 7: Distribution of other antibiotics use in combination with Carbapenem according to diagnosis.

Type of Antibiotic	Chest Infection		Head Infection		Meningitis		Osteomyelitis		Sepsis		UTI	
Amoxicillin-Clavulanic Acid	1	D	0	0		0		0		0		
Azithromycin	1		0	0		0		0		0		
Cefepime	0		0	0		0		1	D	0		
Ceftriaxone	8	D	0	3	D	0		6	D	1	D	
Cefuroxime	1	D	0	0		0		0		0		
Ciprofloxacin	1		0	0		0		0		0		
Doxyxcycline-Ceftriaxone	0		0	0		0		1	D	0		
Levofloxacin	1		0	0		0		0		0		
Levofloxacin-Metronidazole	1		0	0		0		0		0		
Linezolid	0		0	0		0		1		0		
Metronidazole	2		0	1		2		2		1		
Metronidazole-Ceftriaxone	4	D	0	1	D	1	D	2	D	1	D	
Metronidazole-Ciprofloxacin	1		0	0		0		0		0		
Metronidazole-Moxifloxacin	0		0	0		1		0		0		
Moxifloxacin	3		0	0		0		3		1	N	
Moxifloxacin-Ceftriaxone	8	D	0	0		0		2	D	0		
Moxifloxacin-Metronidazole	0		0	0		0		1		0		
Vancomycin	1		1	1		0		0		0		
Vancomycin-Ampicillin	0		0	1	D	0		0		0		
Vancomycin-Ceftriaxone	0		0	1	D		0		0	0		
Vancomycin-Levofloxacin	0		0	0			1		0	0		

D: Therapeutic Duplication; N: Not Recommended

In the current study, carbapenem drugs were administered in 75% of the patients as the first line. Interestingly, the prior use of antibiotics with broad-spectrum coverage, such as carbapenem drugs, was significantly associated with the acquisition of resistance[20]. Carbapenem drugs should be reserved for the treatment of infections due to MDR pathogens[21].

CONCLUSIONS

The study results showed that empiric therapy was prescribed in most cases (91.25%).In addition, about 36.3% of the patients required dosage adjustment according to GFR stages. Dosage adjustment, however, was not done as appropriate, mainly in patients who did not have a stable GFR. The need for interventional actions on carbapenem use is essential in the various units of the hospital. In the present study, the frequency of therapeutic duplication and drug-drug interactions were observed. More stringent controls and the implementation of stewardship principles are necessary to reduce the inappropriate use of carbapenem drugs.

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DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

AUTHOR'S CONTRIBUTION

Alyahawi A: writing original draft, conceptualization. **Alrubaiee G:** methodology, investigation. **Alkaf A:** writing, review, and editing, supervision. Final version of manuscript is approved by all authors.

CONFLICT OF INTEREST

None to declare.

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