



Carbapenem Utilization in Critically Ill Patients

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ABSTRACT

Background: Drug Utilization Evaluation (DUE) studies are designed to evaluate and improve the rational use of medications. DUEs have focused on drugs used in high risk patients such as critically ill cases in this study. 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 meropenem) could increase the risk of multi-drug resistant (MDR) pathogens.

Methods: This study was a prospective and cross sectional study performed at three intensive care units (ICUs) of Shariati hospital, affiliated with Tehran University of Medical Sciences. The study was conducted from April 2012 to May 2013. All of the patients were on imipenem or meropenem as an empiric treatment or based upon microbiology culture results included in the study.

Results: Total of 68 patients in three ICU wards evaluated. The most common diagnosis was Central Nervous System (CNS) infections and meningitis (36.8%). The most common microorganism derived from the patient's specimen was *Acinetobacter* spp. (28%). Overall initial treatment for thirty five patients (51.4%) was justified versus nineteen cases (27.9%) of unjustified. For 14 patients (20.5%) empiric treatment was justified, but continuation of treatment was unjustified.

Conclusion: The result of the study showed that empiric therapy was justified in most cases (72%), but according to the culture results, continuation of treatment in several cases was unjustified (47%).

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Introduction

One of the most important points in health care systems is to evaluate the appropriateness of medication use. Drug Utilization Evaluation (DUE) studies are designed to evaluate and improve the prescribing, administration and the rational use of medications. DUEs have mostly focused on drugs with higher cost, higher utilization volume, relatively narrow therapeutic margin and also

broad spectrum antibiotics. They also stress on drugs used in high- risk patients such as elderly, critically ill, post surgical and cancer patients (1).

Carbapenems are beta-lactam type antibiotics with broad spectrum of activity and coverage of Gram-positive and Gram-negative aerobic and anaerobic bacteria. Like other broad spectrum antibiotics, carbapenems are prescribed as a part of empiric therapy in most serious nosocomial infections (2, 3). 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

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with meropenem, because this agent is not hydrolyzed by DHP I (4, 5).

The incidence of imipenem and meropenem resistance is increasing among Gram-negative pathogens, especially *Acinetobacter* spp. One of the reasons could be the overuse of these broad spectrum antibiotics in hospitalized patients including Intensive Care Units (ICUs) (6). The Intensive Care Unit (ICU) is a potentially hostile environment for the vulnerable critically ill patient. Improving the ICU environment involves education of critical care staff, modification of equipment, and careful consideration to future ICU design. In this study, we reviewed the utilization of these antibiotics in critically ill patients.

Patients and Methods

This study was a prospective and cross sectional study, performed at three ICU wards of Shariati Teaching Hospital, affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study was conducted from April 2012 to May 2013. All of the patients, that were included in the study, were inpatient adults older than 18 years in surgical ICU, medical ICU, and neurosurgery ICU. All of them were treated with imipenem or meropenem as an empiric therapy or based upon the culture results. The patients, who had hypersensitivity to the carbapenems, were excluded from the study.

A standard form for imipenem and meropenem indications was designed based on available guidelines (7, 8). Data were recorded daily on individual form for each patient until the last day of ICU stay. The form included age, sex, diagnosis, duration of hospital stay in ICU, reason of antibiotic treatment, daily laboratory values such as serum creatinine, white blood cells, blood pressure and respiratory rate, culture and antimicrobial susceptibility test results, other antibiotics which were used concurrently with carbapenems, and drugs that have interactions with imipenem or meropenem as ganciclovir and sodium valproate. At the duration of 13 months, 68 patients were included. Their DUE forms were recorded, and appropriateness of imipenem or meropenem usage was evaluated.

Demographic and clinical data were gathered and analyzed using basic descriptive techniques with the statistical program, SPSS-PC (version 20.0). The qualitative variables are presented by their frequency of distribution. The quantitative variables are summarized as mean with standard deviation.

Results

Total of 68 patients in three wards were evaluated, including surgical ICU: 12 (17.6%) patients, medical ICU: 28(42.1%) patients and neurosurgery ICU: 28 (42.1%) patients. Thirty two (47.1%) patients were male and 36 (52.9%) were female. The average age of the patients were 58.5 with standard deviation of 19.0. In our study,

Table 1. Patients' demographic information.

Variables (N=68)	Result
<i>Age – yr</i>	
Mean ± SD	58.5 ± 19.0
Min-Max	21.0-92.0
<i>Gender – n</i>	
Male (%)	32 (47.1)
<i>Weight – kg</i>	
Mean ± SD	72.2 ± 10.8
Min-Max	50.0-95.0
<i>Height – cm</i>	
Mean ± SD	166.2 ± 6.5
Min-Max	155.0-190.0

the frequency of diagnosis were Central Nervous System (CNS) infections and meningitis (36.8%), intra abdominal infections (22%), pneumonia (20.6%) and sepsis (20.6%), respectively. The average duration of imipenem use was 12 days, and for meropenem was 15 days. Table 1 shows patients' demographic information.

All the patients received imipenem or meropenem as an empiric treatment. Sixty one patients (89.7%) were ordered for microbiology culture, but only 70.6% had positive culture results, and the others were negative. Forty three patients (63.2%) were on a carbapenem based on infectious diseases specialist's consult. The most common microorganism derived from the patient's specimen was *Acinetobacter* (29.6%). Other microorganisms isolated from the specimen included *Pseudomonas* (21.1%), *E.coli* (11%) and *Staphylococcus epidermis* (9.3%). Table 2 shows the microbiology culture results.

Thirteen patients (19%) needed dose adjustment due to low weight or increased serum creatinine, but none of them received the appropriate dose. Laboratory results of the patients showed that in 13 cases (19.1%) serum creatinine increased more than 50% from the baseline in 2 consecutive times, so dose adjustment would be necessary.

Figure 1 shows data regarding appropriateness of antibiotic use. The antimicrobial treatment included two criteria: empiric treatment and based on culture result. For both we followed the patients after 5 days of admission (hospitalization). Overall initial treatment for 35 patients (51.4%) was justified versus 19 cases (27.9%) of unjustified. For 14 patients (20.5%) initial empiric treatment was justified, but continuation of treatment was unjustified. On the other hand 49 patients (72.0%) received appropriate dose of antibiotics based on their weights and estimated renal function, but 19 patients (28%) consumed inappropriate dose.

Ten patients (14.7%) had strong possibility for drug

Table 2. Microbiology culture results.

Microorganism(n=118)	Patients on Imipenem	Patients on Meropenem	Total
Acinetobacter Spp.	13	22	35 (29.6%)
Citrobacter Spp.	1	0	1 (0.8%)
E. coli	3	10	13 (11.0%)
Enterococcus Spp.	1	9	10 (8.4%)
Klebsiella Spp.	2	7	9 (7.6%)
Pseudomonas Spp.	4	21	25 (21.1%)
Staphylococcus aureus	3	6	9 (7.6%)
Staphylococcus epidermis	1	10	11 (9.3%)
Staphylococcus hemolytic	1	0	1 (0.8%)
Streptococcus pneumonia	1	3	4 (3.3%)

interaction among imipenem or meropenem with valproic acid, which might increase the risk of seizure. But the valproic acid level wasn't checked for any of the patients. Just one patient received ganciclovir with meropenem, which could increase the risk of seizure.

Discussion

It is an absolute need to establish the DUR subcommittees to evaluate antibiotic usage in all hospital wards. In this study, only in seven patients (10.3%) the microorganism was susceptible to imipenem but not to the other agents. So the clinicians can utilize other antibiotics with narrower spectrum. In 49 patients (72.1%) the infection was acquired after 72hr of admission in the hospital, so this would be a sign of multi-drug resistant (MDR) pathogens for patients. In 9 patients (13.2%) infected by *Acinetobacter*, their clinical symptoms didn't improve and their next culture result didn't get negative, so the clinicians decided to add colistin to patient's antibiotic regimen.

For the initial antimicrobial therapy regimen to account for local bacteriologic patterns, each hospital and each ICU should ideally have their own antibiogram, which is updated at least annually (8). Empiric antibiotic therapy modification should be based on the result of microbial cultures and antibiogram tests as soon as possible (9, 14, 15).

The result of this study shows that empiric therapy was justified in most cases (78%), but continuation of treatment according to the culture result in several cases was unjustified (47%). One of the reasons can be the limitation in the number of infectious diseases specialist employed by the hospital, since the initial empiric therapy seemed to be justified.

In a prospective DUE study of three broad spectrum antimicrobials, cefepime, piperacillin-tazobactam and meropenem, the appropriateness rates of antimicrobials

was increased after the intervention of pharmacist. Similar to our study, the majority of their broad spectrum antibiotic regimen was initiated empirically. Also, the rate of appropriateness was significantly lower for empirically selected treatment than for that tailored based on relevant microbiology results. With heavy use of broad spectrum agents, the risk of multi-drug resistant organisms' emergence would be increased (10).

According to Sakhaiyan *et al.*, studied imipenem DUE in febrile neutropenic patients empirically, dose adjustment wasn't considered for any of patients with low weight or high serum creatinine. Imipenem induced nausea was observed in 59.4% of cases. This result may be due to the rapid infusion of the drug. Like our study, they had several limitations including lack of local guidelines to consider the resistance pattern of the center and appropriate imipenem administration instructions for nursing staff (3).

The study can be an alert for physicians to restrict their antibiotic administrations in unnecessary situations, and to emphasize to dose adjustment for drugs like imipenem when needed, in order to reduce the adverse drug reactions such as seizure. In addition the DUR programs should be performed as a routine program in hospitals to evaluate and improve the quality of patient care, especially antimicrobial agents. The data recorded about inappropriate use of antibiotics must be provided to the physicians to be discussed and optimize their medication orders (11, 12).

In patients with suspected bacterial meningitis, empirical antimicrobial therapy is initiated as soon as possible. The choice of specific antimicrobial agents for targeted or empirical therapy is based on the knowledge of antimicrobial susceptibility patterns of the pathogens (13). In this study empirical antimicrobial therapy was justified in most cases, but the continuation of treatment was unjustified in 73% of patients.

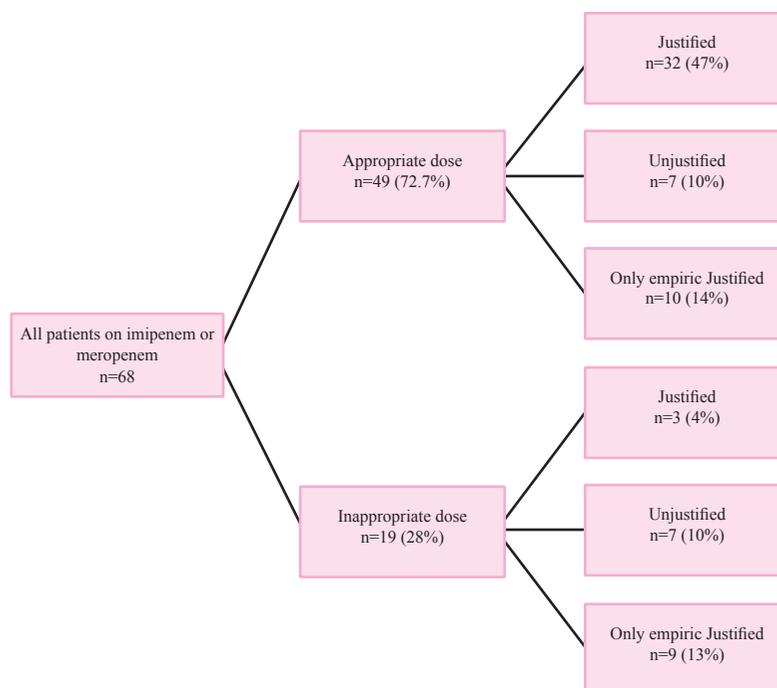


Figure 1. Appropriateness of Antimicrobial Treatment.

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