



## Drug Utilization Evaluation of Imipenem in an Educational Hospital in Mazandaran Province

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### ABSTRACT

**Background:** Imipenem, a member of the carbapenem class of beta-lactam antibiotics, is a broadly active antimicrobial. Due to indiscriminate use, drug resistance has spread in many hospitals. The aim of this study was to evaluate utilization of imipenem in Imam Khomeini educational hospital in Sari. **Methods:** Over a three-month period from September to November 2010, all patients who received imipenem during hospitalization were included. Demographic data, duration of imipenem therapy, dose, dosage adjustment in renal insufficiency and co-prescribed antimicrobials were extracted from patients' medical files. Recommendations of UpToDate 20.2 and Sanford 2009 were considered as standards of rational imipenem prescribing. Data analysis was performed by SPSS 17 software. **Results:** A total of 100 patients with a mean age of 51.4±21.4 were enrolled in the study. Dose and duration of imipenem therapy were appropriate in 64 (64%) and 50 (50%) patients, respectively. In 83 (83%) cases, empiric antibiotic therapy was initiated within the first day of admission which included imipenem in 31 patients (37%). All patients received imipenem as empiric therapy. The most common co-prescribed antimicrobial agent with imipenem was vancomycin (66 cases). Imipenem was administered by consult of an infectious specialist just in 30% of patients. 14 imipenem prescriptions (14%) required dosage adjustment according to the patient's renal function, whereas it was performed only for 5 (35%) patients. Culture tests were carried out for 29 (29%) cases. **Conclusion:** High rate of empiric prescription of imipenem without considering culture and antimicrobial susceptibility results, lack of attention to dosage adjustment in renal insufficiency and initiation of antimicrobial therapy at the time of admission were the most important aspects of irrational use of imipenem that observed in this study. Providing a reliable culture/sensitivity setup and prescribing of imipenem based on a specific guideline are recommended.

### Introduction

Imipenem, a broad spectrum beta-lactam antimicrobial from carbapenem class is indicated for the treatment of serious and life-threatening infections caused by multi-drug resistant microorganisms, where therapeutic alternatives do not exist.<sup>1,2</sup> It is highly active in vitro against most aerobic and anaerobic gram-positive and gram-negative bacteria isolated from infectious diseases of human beings.<sup>3,4</sup> However in recent years due to irrational use, incidence of resistance to imipenem is increasing among Gram-negative pathogens, especially *Pseudomonas aeruginosa* and *Acinetobacter spp.* which have major roles in nosocomial infections. Also the association of

antimicrobial resistance with increased risk of morbidity, mortality, and cost is well documented.<sup>5,7</sup> Numerous reports of irrational use of imipenem and development of resistance in hospitals of various countries around the world including Japan, England, Italy, Greece and Portugal have been published.<sup>8,12</sup> According to the World Health Organization (WHO), rational use refers to receiving the appropriate medication, in the proper dose, for an adequate period of time, and at the lowest cost to them and their community.<sup>13</sup> Five criteria guide appropriate use are: clinical evidence-based therapy, therapeutic benefits, safety, cost-effectiveness and optimal drug dose and

duration in the shorter-course.<sup>14</sup> Therefore, the antimicrobial use is considered rational when it is consistent with the general criteria.<sup>15</sup> One of the studies that facilitates assessment of the appropriateness and rational use of various drugs is Drug Utilization Evaluation (DUE).<sup>16</sup> Although the effectiveness of DUE programs has yet to be established, these studies are still used to identify variability in drug use as well as to support interventions that will improve patients' outcomes.<sup>17</sup> Traditionally, DUE programs have focused on drugs with narrow therapeutic indices, high price tags, complicated dosage schedules and regular side effects.<sup>18,19</sup> Due to lack of information about imipenem prescription in Imam Khomeini hospital, as a referral educational hospital, this study was designed to evaluate the rational use of imipenem in this center. Considering the importance of the imipenem in treatment of infectious diseases and the consequences of irrational use, the present DUE study can help identify defects related to the drug use and then, to develop rational antimicrobial implementation protocols to prevent development of resistance.

## Materials and Methods

This descriptive and retrospective study was approved by the Research Committee of the Mazandaran University of Medical Sciences, Sari, Iran. It was conducted at the general surgery, surgical ICU, general ICU, internal, oncology and obstetrics & gynecology wards in Imam Khomeini educational hospital. The medical records of admitted patients who received imipenem during September to November 2010 were reviewed and entered in data collection forms. Demographic data, diagnosis, antimicrobial therapy received (agents, doses, dose intervals, routes of administration, number of doses, initiation times, and durations of administration) and also details about Imipenem including initiation time, doses, doses intervals, route of administration, dosage adjustments in renal failure, durations of administration, other co-prescribed antimicrobials, drug-prescriber specialty, sample sites and results of culturing and susceptibility test were collected from the patient's medical records. Compliance with the recommendations and defined standards was assessed by the UpToDate 20.2 and Sanford 2009 for every aspect of imipenem use.<sup>20,21</sup>

**Table1.** Demographic and clinical characteristics of the patients(n= 100)

<b>Gender</b>	Male	43 (43%)
	Female	57 (57%)
<b>Age* (years)</b>		51.44 ± 21.44
<b>Length of stay* (days)</b>		18.59 ± 11.94
<b>Diagnosis</b>	Lower respiratory tract infection	21 (21%)
	Urinary tract infections	20 (20%)
	Osteomyelitis	17 (17%)
	Peritonitis	14 (14%)
	Neutropenic fever	7 (7%)
	Septicemia	7 (7%)
	Skin infections	5 (5%)
	Other	9 (9%)
<b>Wards</b>	Surgery	28 (28%)
	Internal	24 (24%)
	Oncology	18(18%)
	General ICU	14(14%)
	Surgical ICU	12(12%)
	Obstetrics and Gynecology	4(4%)

\*Values are presented as mean ± SD.

All the data were coded and SPSS 17 was used for the statistical analysis. The qualitative variables were presented by their frequency and percentage. The Shapiro–Wilk test was used to detect normality in distribution. The quantitative variables were summarized as mean ± standard deviation (SD) or Median (Interquartile Range). Continuous variables between two genders were compared using student's t test and comparing of qualitative data were performed by chi-square test. A p value of less than 0.05 was

considered statistically significant.

## Results

One-hundred patients were included in this study. Mean age of patients was 51.44± 21.44 years (Range 14-87 years). Lower respiratory tract infections, urinary tract infections and osteomyelitis were the most frequent infections, accounting for 21%, 20% and 17% of the diagnosis respectively. Imipenem was prescribed most frequently in surgery (28%), internal (24%) and

oncology (18%) wards. Demographic and clinical data are shown in table 1.

An infectious disease consultation was recorded in about one third of the cases only; however more than four-fifths of the patients (83 %) received first dose of antimicrobial from the first day of hospitalization and also over than thirty percent of patients received imipenem from day 1. Average time elapsed between the patient admissions and receiving first dose of antimicrobials or the first dose of imipenem were 1.69 and 4.64 days, respectively. In male patients,

antimicrobial therapy started earlier than the females; however there was no difference between genders in time of starting imipenem therapy. The mean duration of imipenem therapy was  $11.03 \pm 0.96$  days and in males was significantly longer than females ( $p=0.008$ ); also a trend for longer duration of antimicrobials therapy (including imipenem or other antimicrobials) was noted in males ( $p=0.06$ ). Data associated with antibiotic prescription with emphasis on imipenem are presented in Table2.

**Table 2.** Antibiotic prescribing data according to gender \*

	All patients	Male	Female	P-value
Age (years)	51.5 (42)	50 (39)	52 (44)	0.128
Length of stay (days)	15.5 (20)	20 (29)	13 (13.5)	0.25
Time of starting antibiotic (days)	1 (0)	1 (0)	1 (0)	0.042
Time of starting imipenem (days)	3 (6)	3 (7)	2(4.5)	0.286
Duration of antibiotic therapy (days)	14 (19)	18(23)	11(14.75)	0.064
Duration of imipenem therapy (days)	7 (12)	8 (15)	7(9)	0.008
Dose of imipenem (mg)	1732 $\pm$ 740	1768 $\pm$ 734	1732 $\pm$ 744	0.279
Serum creatinine level (mg/dl)	1.43 $\pm$ 0.54	1.40 $\pm$ 0.63	1.43 $\pm$ 0.47	0.742

\* Values are presented as mean  $\pm$  SD for normally distributed and median (Interquartile Range) for non-normally distributed data.

The most frequently prescribed antimicrobials concomitant with imipenem were vancomycin (66%), fluoroquinolones (37%), aminoglycosides (32%), cephalosporins (12%) and clindamycin (11%), respectively. 64 (64%) patients received appropriate doses, comply with the recommendations and guidelines whereas dosing in 36 (36%) cases was inappropriate and in all of them, patients received doses lower than the recommended dose. Treatment duration with imipenem was 50% appropriate in accordance

with the recommendations. From 50 individuals with improper duration of treatment, 7 patients received imipenem longer than periods justified by guidelines and recommendations. Fourteen patients needed a dosage adjustment due to low weight or renal failure; however only one-thirds of them received correct doses. Overall 39% of hospitalized patients of this center received correct dose of imipenem for proper duration (Table 3).

**Table 3.** Summary of Evaluation of imipenem use in Imam Khomeini Hospital. (n=100)

indices	Appropriate	Inappropriate
Dose (n =100)	64 (64%)	36 (36%)
Duration of therapy (n =100)	50 (50%)	50 (50%)
Dosage adjustment if needed (n=14)	5 (35.7%)	9 (64.3%)
Dose + Duration of therapy (n =100)	39 (39%)	61 (61%)

In 13% of patients adverse events associated with imipenem were observed; the most significant reported complication was seizure which occurred in two patients. All the patients received imipenem as an and for 24.2% up to 72 hours after starting antimicrobial therapy. Samples were collected from urine (14 samples), blood (13 samples), sputum (4 samples), and wounds (2 samples). However culture results were positive in only 8 samples (24.2%) and the others were negative. *E.coli* and *Enterococcus* were isolated from 7 and 1 positive cultures, respectively.

### Discussion

This study was conducted in order to evaluate and improve the rate of appropriate use of imipenem, as a broad-spectrum antimicrobial. Imipenem is indicated

empiric therapy. Clinicians requested cultures fortwenty-nine patients (29%). In 15.2% of cases samples for culture obtained before antimicrobial therapy, for 18.2% it was performed within 24 hours, for the treatment of severe or complicated skin, tissue, joint, respiratory tract, intra-abdominal, urinary tract infections, endocarditis and septicemia and other polymicrobial infections; its use is generally restricted to severe infections mainly in hospitalized patients <sup>22</sup>. Results of this study show that imipenem was mainly used for the treatment of lower respiratory tract infections; in 64% of patients the dose of drug and in 50%, duration of treatment was appropriate. Similar to our findings, in another study Sakhaian et al. showed that in 51.6% of patients undergoing bone marrow transplantation, duration of antimicrobial therapy with

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imipenem was inappropriate; however all patients received appropriate dose of imipenem.<sup>23</sup> Another study in the Amir teaching hospital-Medical University of Zabol also has shown that despite correct dose administration in 96%, duration of therapy was appropriate only in 8%.<sup>24</sup> Inadequate initial antimicrobial therapy in nosocomial infections is associated with developing of antimicrobial-resistance, increased morbidity and mortality rate.<sup>25</sup> For this reason selection of correct antimicrobial with appropriate dose and duration of treatment plays an important role not only in improvement of patient outcomes, but also in the effectiveness of antimicrobials in future infections.<sup>26</sup> The recommended dose of imipenem in adults is 2-4 g/day.<sup>27</sup> Treatment failure, relapse and superinfection are frequent in doses lower than 2g/day.<sup>28</sup> Interesting point in the present study is that all cases of inappropriate dose were associated with prescribed doses lower than 2 g/day; Most of the inadequate dose prescribing occurred in surgery ward (33%). Also best time to discontinue antimicrobial therapy is when the patients' clinical condition show stabilization and fever subsides.<sup>29</sup> The recommended antibiotic therapy duration for imipenem in osteomyelitis is 4 to 6 weeks, in neutropenic fever till the patient is stable and afebrile for at least 24 hours, and the absolute neutrophil count is at least 500 cells/mm<sup>3</sup> and in other indications is between 7 to 14 days.<sup>29</sup> Treatment duration with imipenem was 50% inappropriate in present study. This inappropriate duration was insufficient (43%) or longer than needed (7%). The highest rate of inappropriate therapy duration occurred in surgery wards (40%).

Several studies suggest that males are more susceptible to infections.<sup>30</sup> and rate of infection leading to morbidity and mortality is higher among them.<sup>31-32</sup> In current study we found that despite similar length of stay, dose and Length of antimicrobial therapy between genders, male patients received imipenem longer following initiation of treatment for infection. These seemingly contradictory findings may be related to underlying diseases and severity of infections.

Imipenem therapy has been associated with central nervous system (CNS) toxicity, including change in mental state, myoclonus, and seizures.<sup>33</sup> These effects are especially evident in patients with underlying CNS disease or impaired renal function.<sup>34</sup> The incidence of seizure associated with administration of imipenem is less than 1% for general population and more frequent in patients with neutropenic fever (2%).<sup>31</sup> In present study seizure occurred in 2 patients; the first case was a 17 year old girl who received imipenem with dose of 2g per day over 27 days, concomitant with ciprofloxacin. The second case was a 74 year old male with an estimated creatinine clearance of 51mL/min and history of ceftriaxone prescription before imipenem initiation, received 2 g imipenem daily concomitant with ciprofloxacin over 11 days. It is believed that seizures induced by imipenem may be

directly related to the similarity of the  $\beta$ -lactam ring to the structure of the  $\gamma$ -aminobutyric acid (GABA) neurotransmitter and antagonism at the GABA receptor site.<sup>35</sup> Also ciprofloxacin use may raise seizure risk.<sup>36</sup> Renal dysfunction, history of epilepsy, and increased age are major risk factors for occurrence of ciprofloxacin induced seizures.<sup>37</sup> It has been reported that co-administration of imipenem and ciprofloxacin may increase the risk of CNS adverse events, including seizures.<sup>34</sup>

In summary, our findings highlight the imipenem prescription defects in Imam Khomeini hospital, including high rate of empiric prescription, inadequate dosing in considerable percentage of patients, lack of attention to dosage adjustment in patients with renal failure and initiation of antimicrobial therapy from the first day of hospitalization in high percentage of patients. Sharing and discussing study results with Drug and Therapeutics Committees of hospital, informing the physician from the results of study, paying more attention to sampling, culturing and sensitivity tests and also considering imipenem prescription based on specific protocols are strategies that can be used in order to help to remove the defects observed in this DUE study.

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