

## Clinical Study

### Drug use evaluation of Meropenem at a tertiary care university hospital: A report from Northern Iran

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#### ABSTRACT

**Objective:** The inappropriate use of antibiotics remains the primary factor in antimicrobial drug resistance. In this study, we evaluate the use of meropenem in surgical/medical wards of Imam Khomeini Tertiary Referral Hospital, Sari, Iran.

**Methods:** This retrospective observational study was used to assess rational use of meropenem. The study was conducted by reviewing medical records of 100 admitted patients who received meropenem during March 2013 to January 2014.

**Findings:** Meropenem was prescribed most frequently in Intensive Care Unit (22%), and pneumonia was the most common diagnosis (35%). The third-generation cephalosporins were the most frequently prescribed antimicrobials after meropenem (53%). In 21% of the patients, imipenem was changed to meropenem. Most of the inappropriate uses were seen in terms of frequency of meropenem use (34%), followed by duration of meropenem therapy (28%).

**Conclusion:** Comparing our study results has shown higher inappropriate use. It is necessary to take action to improve prescribing habit in order to reduce the unnecessary usage of antibiotic thus enhance rational antibiotic use.

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## INTRODUCTION

Antibiotics are the most frequently prescribed drugs among all hospitalized patients. About one-third of hospitalized patients receive antimicrobial therapy.<sup>[1]</sup> However, excessive and inappropriate use of the antibiotics remains the primary factor in the emergence and spread of antibiotic-resistant bacteria.<sup>[2]</sup> Optimizing medication utilization has the potential to reduce the development of antimicrobial

resistance and to lower overall health care costs by providing cost-effective treatments.<sup>[3]</sup>

As one of the broad-spectrum antibiotics, meropenem is widely used to treat a wide variety of infections.<sup>[4]</sup> It is considered as a potent drug for treatment of multidrug resistant Gram-negative infections due to the stability of these agents against the majority of beta-lactamases and their high rate of permeation through bacterial outer membranes. However, there have been reports of

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the emergence of resistant to meropenem.<sup>[5,6]</sup> A recent study reported an emergence of imipenem-susceptible, meropenem-resistant *Klebsiella pneumoniae*.<sup>[7]</sup> The high incident of empirical prescription for this drug in hospitals will potentially increase the prevalence of resistance, making it an important candidate for execution of drug use evaluation (DUE) studies. The aim of this study was to evaluate the use of meropenem in Imam Khomeini Hospital located in Mazandaran Province, Sari, Northern Iran, to provide an overview of its use in hospital in order to promote the rational prescribing, dispensing, and administration of meropenem.

## METHODS

This retrospective observational study of meropenem usage was approved by the Ethics Committee of Mazandaran University of Medical Sciences and was conducted in the General Surgery, Surgical Intensive Care Unit (ICU), Medical ICU, Internal, Oncology, Orthopedic, Urology, Neurology and Obstetrics and Gynecology Wards of Imam Khomeini Hospital, Sari, Iran. Imam Khomeini Hospital is a Teaching Hospital Affiliated to Mazandaran University of Medical Sciences and is a 300-bed referral and Tertiary Care Hospital in North of Iran. The medical records of admitted patients who received meropenem during March 2013 to January 2014 were reviewed.

Demographic data, antibiotic medication history (agents, doses, dose intervals, routes of administration, number of doses, initiation times, and durations of administration), site(s) of infection, indication of meropenem use, initiation time, dosing regimen, rate and duration of administration, other co-prescribed antimicrobials, meropenem prescriber's specialty, renal function status, and microbiology laboratory results were collected and recorded in data gathering form. Analysis of the appropriateness of the use of meropenem was evaluated based on recommendations provided by American Hospital Formulary Services<sup>[8]</sup> and the Sanford Guide to Antimicrobial Therapy. Meropenem has approved indication for complicated skin/skin structure infections and intra-abdominal infections. It also has off-label indication for community-acquired pneumonia and febrile neutropenia. The appropriate use of meropenem requires considering appropriate dose, frequency, and duration of treatment. The usual dose for most of the indications is 500–1000 mg, every 8 h, and the maximum recommended dose is 2 g intravenous, every 8 h. The dose should be modified in renal impairment.<sup>[9]</sup>

Data were gathered and analyzed using the statistical software, SPSS (Version 19, IBM Corporation, Armonk, NY, USA), the qualitative variables are presented by

their frequency of distribution. The quantitative variables are summarized as mean with standard deviation.

## RESULTS

Meropenem was given to 153 adult hospitalized patients from August March 2013 to January 2014. One hundred of 153 patients were included in the study based on their medical record number randomly selected by "random number table." Sixty-three of patients were male. Mean age of patients was  $47.6 \pm 20.7$  years (range 14–83 years) [Table 1].

Meropenem was prescribed most frequently in ICU (22%), followed by oncology (19%), surgical (19%) and internal medicine (17%) wards. In 35% of the cases, meropenem was prescribed for pneumonia.

Mean duration of hospitalization was  $15.6 \pm 11$  days (range 2–55 days). In 63% of the hospitalized patients, antimicrobial therapy was started from the 1<sup>st</sup> day of admission. The mean duration of antimicrobial therapy was  $13.5 \pm 10.6$  days. In addition to meropenem, patients received  $2.75 \pm 1.47$  antibiotics during their hospital stay [Table 2]. Third generation cephalosporins (53%)

**Table 1: Demographic and clinical characteristics of the patients (n=100)**

Variable	Frequency (%)
Age (years)	
<20	9 (9)
20-39	34 (34)
40-59	21 (21)
>60	36 (36)
Sex	
Male	63 (63)
Female	37 (37)
Diagnosis	
Pneumonia	35 (35)
UTI	15 (15)
CNS infections	15 (15)
Dermal infections	10 (10)
Fever in neutropenic patients	10 (10)
Other	15 (15)

UTI=Urinary tract infection, CNS=Central nervous system

**Table 2. Antibiotic prescribing data (n=100)**

Variable	Mean±SD
Length of hospital stay (days)	15.6±11
Time of starting antibiotic (days)	2.7±3.7
Duration of antibiotic therapy (days)	13.5±10.6
Time of starting meropenem (day)	6.7±5.6
Duration of meropenem therapy (days)	7.3±6.7
Dose of meropenem (mg)	2.06±0.88

SD=Standard deviation

and vancomycin (52%) were among the most frequently prescribed antimicrobials. In 21% of the patients, imipenem was changed to meropenem and in 1 case it was due to imipenem induced seizure.

An infectious disease consultation was recorded in 52% of the cases. The renal function tests were evaluated in 96% of patients. Nine patients had abnormal results, and only three of them received dosage adjustment based on their renal function. The prescribed daily dose of meropenem for each patient was  $2.06 \pm 0.88$  g [Table 2]. Patients received  $1.32 \pm 0.84$  antimicrobial agent concomitant with meropenem.

All the patients received meropenem as an empiric therapy. Microbiological cultures were utilized in the course of therapy for 38% of patients receiving meropenem. In 34.4% of the cases, samples for culture obtained before antimicrobial therapy, for 15.6%, it was performed within 24 h after starting antimicrobial therapy. The most common isolated micro-organisms were *Acinetobacter* spp., *Escherichia coli*, *Enterococcus* spp., and *Pseudomonas aeruginosa*. Antibioqram was performed only for three of them.

It was found that 95% of meropenem indications were appropriate, 92.5% and 52.5% of indications contained correct dose and frequency of the drug respectively, in 51.6% of the patients, the antibiotic therapy duration was not appropriate [Table 3].

## DISCUSSION

This study provides the data on the use of meropenem in patients admitted to surgical/medical wards of Imam Khomeini Hospital. Previously we evaluate the rational use of imipenem in this center.<sup>[10]</sup> Meropenem and imipenem are two carbapenems with similar spectrum.<sup>[11]</sup> However, important differences exist between the two compounds in favor of meropenem.<sup>[12]</sup> These include the greater *in vitro* activity of meropenem against the predominant Gram-negative pathogens<sup>[11]</sup> and its stability to renal dehydropeptidase-I (DHP-I), which permits its administration without a DHP-I inhibitor

**Table 3: Distribution of appropriate use of meropenem based on DUE criteria (n=100)**

Indices	n (%) of appropriate cases
Indication	92 (92)
Dose	75 (75)
Frequency	66 (66)
Duration	72 (72)
Indication + dose + frequency + duration	41 (41)

DUE=Drug use evaluation

such as cilastatin (which can accumulate in renal failure).<sup>[13]</sup> Also, meropenem is well-tolerated by the central nervous system with regard to seizures.<sup>[12]</sup>

In our study, appropriate meropenem use obtained in only 41% of the patients. Previous studies evaluating meropenem use in hospitals have reported that 21–46.5% of prescriptions can be inappropriate.<sup>[14-17]</sup> Comparing our study results has shown higher inappropriate use. In our study, most of the inappropriate prescribing occurred in surgery ward. Surgeons might be a suitable primary target for the interventional studies. The panel discussions including different specialties, seminars, and pamphlets about antimicrobial decision making and antimicrobial rational use will be helpful.<sup>[3]</sup>

Our results show that meropenem therapy was started for all patients based on empiric therapy, and microbiological cultures were utilized only for 38% of the patients. It seems to be reasonable to promote practice guidelines about utilizing culture and sensitivity testing when considering the use of broad spectrum antibiotic like meropenem. Also in our study, antibiotic recommendations by infectious disease specialist consultation were done for 52 patients despite its rate is much higher than the rate of imipenem consultation.<sup>[10]</sup> Our hospital should consider guidelines regarding broad-spectrum antimicrobials, which include a requirement of an infectious disease consultation prior to initiation of these drugs.

We performed a DUE study for meropenem and attempted to gather basic data to examine the appropriate use of antibiotics. Our findings highlight the meropenem prescription defects in Imam Khomeini Hospital, including high rate of empiric prescription, lack of attention to dosage adjustment in patients with renal failure, initiation of antimicrobial therapy from the first day of hospitalization in high percentage of patients, and inadequate culture and sensitivity tests.

## AUTHORS' CONTRIBUTION

Salehifar designed the study and contributed in data analysis and revising the manuscript; A. Shiva supervised data collection and contributed in data analysis and writing the initial draft of the manuscript; M. Moshayedi contributed in data collection and contributed in writing the initial draft of the manuscript; T. Samiei Kashi and A. Chabra contributed in data collection.

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**Conflicts of interest**

There are no conflicts of interest.

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