

Original Article

Meropenem Utilization Evaluation in a Referral Teaching Hospital in Iran

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INTRODUCTION

Inappropriate use of antibiotics is associated with detrimental effects including emergence of antibiotic resistance affecting treatment outcome.^[1] The Centers for Disease Control and Prevention estimated 23,000 deaths/year in the USA due to infections by antibiotic-resistant pathogens.^[2] Therefore, curbing antibiotic resistance is a major public health priority.^[3]

Epidemiological studies have shown a link between carbapenem use and resistance.^[4] Carbapenem-intermediate or -resistant Enterobacteriaceae, including *Klebsiella pneumoniae*

ABSTRACT **Objective:** Inappropriate use of antibiotics is associated with detrimental effects including emergence of antibiotic resistance. This study aimed to evaluate the use of meropenem, an extended-spectrum antibiotic, in a referral teaching hospital to detect different types of errors in its prescription. **Methods:** In a cross-sectional study performed over a 6-month period (2014–2015), hospitalized adult patients who received meropenem for any indication were randomly selected. The collected data included the indication for prescription and its correctness, the basis of prescription (empirical or culture based), administered dose, duration of treatment, the status of demanding sample culture in the case of empirical prescription, the status of dose adjustment in the case of renal impairment, and the treatment outcome. **Findings:** Over the study period, 123 patients were evaluated. The most frequent indication for prescription of meropenem was pneumonia (31.7%) and soft-tissue infections (18.7%). Out of these prescriptions, 62.6% (77 prescriptions) were incorrect. All meropenem prescriptions were initially empirical. Furthermore, sample culture and antibiotic susceptibility test were requested for only 52% of patients ($n = 66$). Treatment duration was correct for 53.7% of patients. Seventeen patients (13.8%) received an inappropriate dose of the antibiotic. Furthermore, of 51 patients who needed meropenem dose adjustment because of renal impairment, 17 patients (33.33%) received unadjusted dose. **Conclusion:** High rate of errors exists in the utilization of meropenem in our hospital, especially in the rank order of selection for treatment (indication), dose adjustment, and treatment duration. Therefore, modification strategies are necessary to promote the rational use of meropenem in this center.

KEYWORDS: Drug utilization evaluation, hospital, Meropenem

carbapenemase-producing bacteria, are of increasing concern and have rapidly spread globally.^[5-7]

Meropenem, a parenteral carbapenem antibiotic, has a broad spectrum of antibacterial activity *in vitro* with the majority of Gram-negative, Gram-positive, and anaerobic pathogens being highly susceptible to the drug.^[8] Meropenem is likely to have the greatest value for empiric treatment of serious infections or those caused by multidrug-resistant pathogens.^[8]

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Due to resistance to destruction by most β -lactamase enzymes, carbapenems are often used as last-line therapy for infections due to multidrug-resistant Gram-negative bacilli.^[9] However, there has been an alarming emergence of carbapenem-resistant bacteria including *Acinetobacter* spp.^[10,11] and *Pseudomonas aeruginosa*^[12,13] over recent years.

Drug utilization studies are performed to analyze management data obtained over a certain period of time or to evaluate the effects achieved by therapeutic interventions. Moreover, the patterns of use are evaluated to obtain the information necessary to devise and update prescribing policies as well as to provide proper feedback to the prescribers.^[14] The high rate of empirical prescription of meropenem in hospitals will potentially increase the prevalence of resistance, making it an important candidate for drug utilization evaluation (DUE) studies.^[15] Therefore, this study was conducted to evaluate the use of meropenem in a referral teaching hospital of Isfahan, Iran, to detect different types of errors in its choice, prescription, and administration to informing the health-care providers of these errors to correct them and prevent subsequent ones and improve meropenem use pattern.

METHODS

This was a descriptive cross-sectional study performed over a 6-month period from September 2014 to March 2015 in Alzahra Teaching Hospital affiliated to Isfahan University of Medical Sciences. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences. The study population was adult patients (>18 years) hospitalized in any hospital ward except for the Intensive Care Units (ICUs) that were prescribed meropenem for any indication. The patients were identified using the computerized information system of the hospital's pharmacy. For random selection of patients from the obtained list, the last two digits of the medical record code and the random number table were used. The collected data for each patient included demographic characteristics (age and sex), hospitalization ward, the indication for prescription of meropenem (initial diagnosis) and its correctness, the basis of prescription (empirical or based on the culture results), administered dose and its correctness,^[16] duration of treatment with meropenem and its correctness, the status of demanding sample culture in the case of empirical prescription, creatinine clearance (calculated using Cockcroft-Gault formula) and the status of dose adjustment in the case of renal impairment ($\text{CrCl} \leq 50$ ml/min),^[16] concurrent antibiotics, receipt of interacting drug (any preparation of valproic acid or sodium valproate),^[16]

the specialty of prescribing physician, and the treatment outcome, recorded as clinical response, nonresponse, or death. Clinical response was defined as improvement in all infection symptoms, no symptom worsening, and clinical stability for at least 24 h. Clinical judgment about the correctness of the indication for meropenem use, the administered dose, and treatment duration in each patient was made using the related clinical practice guidelines (if present) and reliable textbooks.^[17-19] In this case, the expert opinion including the judgment of two infectious disease specialists and an infectious disease clinical pharmacist was also considered.

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For each variable, the frequency distribution and the corresponding percentages were determined.

RESULTS

Over the study period, 123 patients were evaluated regarding meropenem utilization that 63.4% of whom were male. The mean \pm standard deviation age of patients was 54.65 ± 18.72 years. The most meropenem prescriptions were for age group of 45–75 years ($n = 68$, 55.28%), followed by groups of 25–35 years ($n = 18$, 14.63%), 75–85 years ($n = 13$, 10.57%), 18–25 years ($n = 10$, 8.13%), 35–45 years ($n = 9$, 7.32%), and 85–95 years ($n = 5$, 4.06%).

Regarding hospital wards, most patients were from infectious diseases and nephrology/rheumatology wards (each, $n = 28$), followed by pulmonary diseases ($n = 24$), gastroenterology ($n = 12$), vascular surgery and men surgery (each, $n = 5$), men and women orthopedic, and neurology (each, $n = 4$), cardiology ($n = 3$), obstetrics and gynecology ($n = 2$), and plastic surgery, women surgery, neurosurgery, and thoracic surgery (each, $n = 1$) wards.

The most frequent indication for prescription of meropenem was pneumonia ($n = 39$, 31.7%), skin and soft tissue infections ($n = 23$, 18.7%), and urinary tract infections ($n = 21$, 17.1%) followed by intra-abdominal infection ($n = 5$, 4.1%), sepsis and bacterial meningitis (each, $n = 4$, 3.3%), cholecystitis ($n = 3$, 2.4%), and fever and neutropenia and fever of unknown origin (each, $n = 2$, 1.6%). Twenty patients (16.3%) had no distinct diagnosis. Out of these prescriptions, 62.6% (77 prescriptions) were incorrect. Table 1 shows the frequency distribution of correct and incorrect meropenem prescriptions in the four hospital wards with the most evaluated patients. As shown, pulmonary diseases and nephrology/rheumatology wards had the most and the least cases of incorrect prescriptions, respectively.

All meropenem prescriptions were initially empirical. Furthermore, sample culture and antibiotic susceptibility test were requested for only 52% of patients ($n = 66$) with only 2 of these patients (3.03%) being underwent antibiotic regimen change based on the tests results.

The mean duration of treatment with meropenem was 9.3 ± 4.3 days (the range of 1–30 days) with 53.7% of patients being treated with correct duration.

In terms of prescribed dose, 106 patients (86.2%) received the correct dose of meropenem based on the indication, whereas 17 patients (13.8%) were administered an inappropriate dose of the antibiotic. Furthermore, of 51 patients who needed meropenem dose adjustment because of renal impairment, 17 patients (33.33%) received unadjusted dose.

Regarding concurrent antibiotics, 75.6% of patients ($n = 93$) received one or more antibiotics with meropenem (average number of 1.42 ± 1) as follows: one antibiotic for 44 patients, two antibiotics for 36 patients, three antibiotics for 17 patients, and four antibiotics for 2 patients. Vancomycin (39%), teicoplanin (17.1%), levofloxacin (13%), and ciprofloxacin (11.3%) were the most frequently prescribed concurrent antibiotics with 19.5%, 4.9%, 12.2%, and 8.9%, respectively, of their prescriptions being incorrect.

Over the study period, 11.4% of evaluated patients ($n = 14$) received the interacting drug with meropenem, sodium valproate, while no one underwent serum valproate level monitoring for dose adjustment.

Figure 1 shows the frequency distribution of correct and incorrect prescriptions of meropenem (regarding the indication) by different medical specialists. As shown, most prescriptions were made by internists ($n = 36$), infectious diseases specialists ($n = 33$), pulmonologists ($n = 19$), and nephrologists ($n = 17$) with 77.8%, 30.3%, 78.9%, and 64.7%, respectively, of prescriptions being incorrect.

In terms of treatment outcome, of 123 evaluated patients, 111 patients (90.24%) had a clinical response to the treatment, whereas 12 patients (9.76%) did not achieve clinical response and no one died of infection.

DISCUSSION

Our results in the present study show a high rate of errors in meropenem utilization in our referral teaching hospital. In Iran, few studies have focused merely on meropenem DUE. In a study performed at Imam Khomeini hospital of Sari,^[15] the appropriate use of meropenem was reported in only 41% of patients that is relatively

similar to our result (37.4%). For better comparison, Table 2 shows the obtained values of different evaluated variables in the two studies. Considering the high rate of error in obtaining microbial culture in the two studies, it seems that appropriate strategies should be designed for adequate attention to this stage of antibiotic therapy since many empirical treatments of infections should be adjusted or de-escalated based on the sample culture results if necessary.^[20-22] However, in our study, only two patients (1.62%) underwent antibiotic change based on the culture results.

In another study conducted in three ICUs of Shariati Hospital of Tehran, carbapenems' (imipenem and meropenem) utilization was evaluated in critically ill patients.^[23] The comparison of the results of this study with those of our work is presented in Table 3. As shown, a higher rate of correct prescription was observed in the mentioned study. This could be due to the difference of study populations, as most critically ill patients need extended-spectrum antibiotics, including carbapenems, for treatment of their infection.

Several DUE studies of meropenem have been performed in other countries. In a study in Pakistan, only 40% of empirical meropenem prescriptions were appropriate.^[24] This is similar to both our and Sari studies' results. In another study conducted in Thailand, 95.7% of meropenem prescriptions agreed

Table 1: Frequency distribution of correctness of meropenem prescription in the four hospital wards with the most evaluated patients

Ward	Correct	Incorrect
Nephrology/rheumatology	16 (57.2)	12 (42.8)
Infectious diseases	15 (53.6)	13 (46.4)
Gastroenterology	6 (50)	6 (50)
Pulmonary diseases	4 (16.7)	20 (83.3)

Data are presented as n (%)

Table 2: Comparison of the results of meropenem drug utilization evaluation studies in Alzahra (present study) and Imam Khomeini Hospitals

Variable	Imam Khomeini Hospital, Sari	Alzahra Hospital, Isfahan
The most frequent indication (%)	Pneumonia (35)	Pneumonia (31.7)
Correct indication (%)	41	37.4
Need for dose adjustment (%)	5.9	41.5
No dose adjustment (%)	77.8	33.4
Empirical initial prescription (%)	100	100
Obtaining microbial culture (%)	38	48
Correct duration of treatment (%)	51.6	53.7
Average number of concurrent antibiotics	1.32 ± 0.84	1.42 ± 1

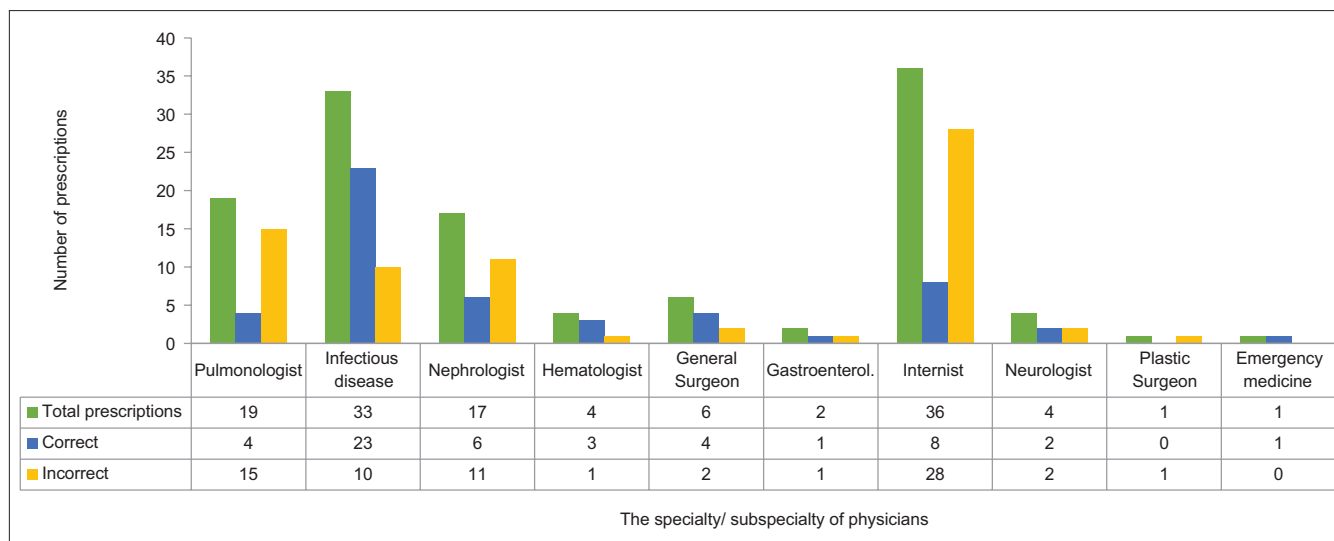


Figure 1: Frequency distribution of correct and incorrect meropenem prescriptions by different medical specialists during the study

Table 3: Comparison of the results of meropenem drug utilization evaluation studies in Alzahra (present study) and Shariati Hospitals

Variable	Shariati Hospital, Tehran	Alzahra Hospital, Isfahan
The most frequent indication (%)	Meningitis (38.8)	Pneumonia (31.7)
Correct indication (%)	51	37.4
Need for dose adjustment (%)	19	41.5
No dose adjustment (%)	100	33.4
Empirical initial prescription (%)	100	100
Obtaining microbial culture (%)	89.7	48
Correct dose	72	86.2

with indication criteria according to the guideline.^[25] Furthermore, higher rates of performing microbial culture and antibiotic susceptibility test were reported in this study (96.6%) compared to ours (52%).^[25] However, the rate of correct prescribed dose was similar (81% vs. 86% in our study) indicating low frequency of this type of error in our medical center.

As expected, infectious disease specialists had the least errors in meropenem prescriptions in our study. Therefore, consultation with an infectious disease physician can improve the rational use of antibiotics including extended-spectrum antimicrobials. Furthermore, consultation with an infectious disease clinical pharmacist can promote the rational use of drugs including antimicrobials, as several studies have reported the role of these specialists in the improvement of drug use including reduction in the cost of therapy, minimizing polypharmacy, and reduction in unnecessary prescribing of antimicrobials.^[26-28]

Regular educational programs about various aspects of antimicrobial therapy, including updated treatment

guidelines, dosing principles, and serious effects of irrational use of antibiotics in the emergence of microbial resistance, can be an effective way for improvement of antibiotics use. In a DUE study, meropenem appropriate use raised from 79% to 89% with 1 month of education.^[29] Furthermore, in an educational intervention among professionals, the use of bacterial culture and sensitivity tests improved by 88.29% from 65.22% and the correct indication rate improved to 94.59% from 84.38% after 1 month education course.^[30]

High rate of errors exists in the utilization of meropenem in our referral hospital, especially in rank order of selection for treatment (indication), dose adjustment, and treatment duration. Therefore, modification strategies are necessary to promote the rational use of meropenem in this center.

AUTHORS' CONTRIBUTION

P. Naderi performed data collection. R. Soltani interpreted the collected data regarding correctness and analysed them. K. Shirani and F. Khorvash interpreted the results regarding correctness. S. Naji Esfahani drafted the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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