RESEARCH PAPER

The Role of Clinical Pharmacists in Optimizing Meropenem Therapy in the ICU

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ABSTRACT

Background: Meropenem is broadly consumed in intensive care units for severe, multidrug-resistant infections and sometimes even as prophylaxis in critically ill patients. Still, the effectiveness and prescribing appropriateness are a major concern due to a lack of dose adjustment and dosing frequency, especially in renal impairment.

Aim: The objective is to identify current meropenem prescribing patterns in terms of appropriateness, indication status, dosing, dosing frequency, renal adjustment, infusion strategy, and microbial culturing by assessing clinical response after 48 hours in ICU patients. Then recognize the areas where clinical pharmacists can optimize the therapy.

Methods: 120 adult ICU patients were enrolled in a prospective observational study who received meropenem therapy. Clinical, microbiological, and laboratory data were recorded at the initiation and after 48 hours of meropenem use. To explore the associations between renal function, appropriateness variables, and outcomes, statistical analysis included non-parametric statistical analysis.

Results: We noticed meropenem was frequently inappropriately prescribed, with errors in indication, dosing, and renal adjustment commonly in patients with impaired renal function, and almost all of the patients received their therapy by short infusion. In general, the treatment was successful in reducing inflammation, but the reduction in the markers was more pronounced when meropenem was used appropriately and by antimicrobial stewardship standards.

Conclusion: Despite the frequent use of Meropenem in the ICU, it was mostly accompanied by several prescribing errors, especially in patients with moderate to severe kidney function, which included inappropriate and incorrect usage, in cases of indication, dose, and dosing frequency, regardless of the early (48-hour) clinical results. The non-consistent antimicrobial stewardship practice in the setting highlighted the risk of future carbapenem resistance. The findings underscored the urgent need for specialized clinical pharmacists to focus on optimizing meropenem prescribing.

Keywords: *Meropenem, ICU, Appropriate, Role of Clinical Pharmacist, Inflammatory Markers*
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INTRODUCTION

Meropenem belongs to the carbapenem group of antibiotics and is one of the potent treatment options available today. It's widely used in ICU units due to its broad-spectrum coverage; extensively active against Gram-negative and some Gram-positive bacteria, availability in a parenteral dosage form, ideal pharmacokinetic/pharmacodynamics profile, and time-dependent bactericidal activity make it one of the best options in the management of critical cases like severe sepsis and multidrug-resistant infections. (1)

However, researches show that there's inappropriate antibiotic prescription in hospitals as much as 50%, (2) including unjustified prescription, sub-therapeutic dosing, or unnecessary elongation of therapy, in addition to that there's an increase trending of using this drug as an empirical therapy and some senior doctors prescribe it as a prophylaxis for the

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prevention of nosocomial infection, which increases the risk of carbapenem resistant organisms and limits future treatment options. Therefore, optimizing the use of meropenem is essential not only for patient outcomes but also to prevent antibiotic resistance in the region.

Generally, critically ill patients in the ICU have altered physiological changes, a change in volume of distribution, modified renal function, and end-organ damage, and prior nephrotoxic medications that have profound pharmacokinetic effects on drugs. (3) Renal impairment is a particular issue that needs to be considered carefully when administering Meropenem because it has a direct effect on its clearance and requires adjustment to avoid further harm, such as toxicity to the already ill patient. (4) Properly structured prescribing, aligned with the terms of global antibiotic stewardship programs, is essential to avoid future resistance, reduce healthcare costs, and improve patient outcomes. (5)

The ICU team consists of a multidisciplinary team with Clinical pharmacists increasingly important role in medication review and patient follow-up, renal dosing, therapeutic drug monitoring, assessing adverse effects, and antimicrobial stewardship. (6) However, on many occasions, pharmacists are reframed in a passive role and unengaged in clinical decision-making; they are given a medication-dispensing-focused role. But in the ICU, the pharmacist's role is crucial, where the patients are critically ill, and their medication must be carefully analyzed. In addition to that, antibiotic consumption like meropenem requires extra regulation in the settings and must be under the supervision of a clinical pharmacist (7)

In our study, we wanted to assess current practice in Meropenem prescription in the ICU and evaluate the pharmacists' role in managing this therapy. We aim to find the patterns and pitfalls regarding this matter and find pharmacists role in preventing and robusting the treatment.

METHODS

Study Design and Setting

A prospective observational study was conducted starting from 1st of June to 1st of December aiming to identify and evaluate clinical characteristics, laboratory parameters, and prescribing patterns linked to meropenem treatment among patients admitted to the intensive care unit (ICU) of a tertiary care hospital. After the Ethical consents were received from the hospital administration, the ICU department, and the patient's family, data were collected from patients according to the paper code (15) who received meropenem as part of their treatment for suspected or confirmed infections.

Sample size and study population

During the period of this research, approximately 360 patients were admitted to the ICU, 183 of them were prescribed meropenem therapy, and among them, 120 patients were selected to enroll in the study according to our inclusion criteria.

Inclusion criteria: patients aged ≥18 years admitted to the ICU, receipt of meropenem for 48 hours, and the availability of clinical and laboratory data.

Exclusion criteria: patients younger than 18 years, those receiving meropenem outside the ICU, patients with incomplete data, patients discharged before adequate clinical evaluation, critically ill patients who were expected to pass away, and pregnant patients.

Data collection

Standardized data collection forms were designed to gather patient information from their medical records, laboratory results, and medication charts.

The information was taken when first administered meropenem, and later, after 48 hours, the same data were gathered during the ongoing treatment to assess the usefulness of the treatment.

The collected information included:

1-Demographic characteristics: age, gender, and body weight

2-Clinical characteristics: primary diagnosis, infection site, and comorbidities

3- Meropenem therapy characteristics: indication, dose, dosing frequency, route of administration, infusion duration, dose modification after 48 hours, and antibiotic switching

4-Microbiological data: culture and sensitivity testing results

5-Laboratory parameters: serum creatinine, blood urea, CRP, and complete blood count

Renal function was calculated using the estimated glomerular filtration rate (eGFR) based on serum creatinine.

Evaluation of Appropriateness of Meropenem Treatment

The appropriateness of meropenem prescription was assessed upon clinical indication, dosing regimen, and infection features according to international antimicrobial therapy guidelines.

Therapy was categorized as:

1- Appropriate therapy: meropenem prescribed according to recommended indications and dosing guidelines.

2- Inappropriate therapy: meropenem prescribed without a clear indication, incorrect dosing regimen, or unnecessary prophylactic use.

Evaluation was according to recognized antimicrobial treatment guidelines, such as the Sanford Guide to Antimicrobial Therapy and the Infectious Diseases Society of America (IDSA) recommendations.

Statistical Analysis

Statistical analysis was performed using nonparametric tests and chi-square tests. Continuous paired data (e.g., changes in laboratory parameters before and after meropenem therapy) were analyzed using the Wilcoxon signed-rank test. Comparisons of renal function (rGFR) across antibiotic regimen groups were conducted with the Kruskal–Wallis test. Associations between categorical variables, such as renal impairment category, indication appropriateness, dose correctness, dosing frequency correctness, infection site, and culture performance, were evaluated using chi-square tests or Fisher's exact test when expected cell counts were small. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted according to code paper (15) and the ethical principles outlined in the Declaration of Helsinki for medical research involving human subjects. Approval for the study was obtained from the institutional ethics committee/ Koya University, and verbal informed consent was obtained from the patient or their family. Patient confidentiality and privacy were preserved throughout the study, and all patient identifiers were removed during analysis.

RESULTS

Infusion duration and laboratory response

In Figure 1, it's shown that only 4 (3.3%) patients received meropenem with 180-minute infusion, whereas the remaining 116 (96.7%) were treated with 30-minute infusion. Owing to the very small sample size, no statistical analysis was performed for comparison, because in this case, the result would not reflect the scientific fact, and interpretation would be biased and not reliable.

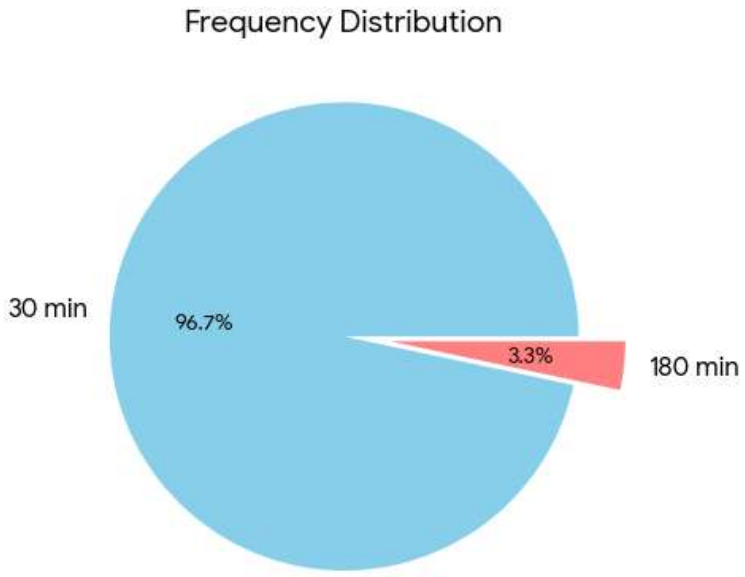

Figure 1: Distribution of infusion duration among patients

Appropriateness of Meropenem use and Inflammatory Markers

As shown in Table 1, there was a significant reduction in the inflammatory markers in all the patients, i.e., those who were prescribed appropriately as well as those who were not appropriately prescribed. While the reduction in those who were appropriately prescribed ("Yes") was much more pronounced where CRP was ($p < 0.001$), and WBC also decreased significantly ($p = 0.004$) but in the inappropriately prescribed patients ("No"), CRP decreased ($p < 0.001$) and WBC counts declined ($p = 0.016$), which is also significant but considerably less than the former.

Table 1: Effect of medication use appropriateness on inflammatory markers

Variable	Appropriate	Negative Ranks n (%)	Positive Ranks n (%)	p-value
CRP (mg/l)	No	64 (74.4%)	22 (25.6%)	<0.001
	Yes	26 (92.9%)	2 (7.1%)	<0.001
WBC	No	56 (62.2%)	34 (37.8%)	0.016
	Yes	22 (73.3%)	8 (26.7%)	0.004

Treatment by Disease Indication Status

Similarly, the inflammatory markers were decreased in all of the patients who took meropenem, regardless of being "indicated" or "not indicated". While the reduction in the "indicated" patients was much more pronounced as shown in the table 2 below where the reduction CRP showed a stronger decrease ($p < 0.001$) and WBC also decreased more significantly ($p = 0.005$) but in the "not indicated" patients, CRP decreased less significantly ($p = 0.006$) and WBC decreased less modestly ($p = 0.046$) compared to the former.

Table 2: Effect of Treatment by Disease Indication Status

Variable	Indication Status	n (%)	p-value
CRP(mg/l)	Not indicated	30 (75.0%)	0.006
		10 (25.0%)	
	Indicated	60 (81.1%)	<0.001
		14 (18.9%)	
WBC	Not indicated	28 (63.6%)	0.046
		16 (36.4%)	
	Indicated	50 (65.8%)	0.005
		26 (34.2%)	

Renal function, concomitant antibiotics, and eGFR

A Kruskal–Wallis test revealed a statistically significant difference in eGFR across antibiotic regimens ($H = 7.692$, $p = 0.021$). Patients receiving meropenem had the highest mean eGFR rank, followed by those receiving meropenem with other antibiotics; the lowest mean rank was observed in patients treated with meropenem plus vancomycin (mean ranks: 71.37, 58.28, and 52.29, respectively). These findings indicate variation in renal function among different antibiotic combinations.

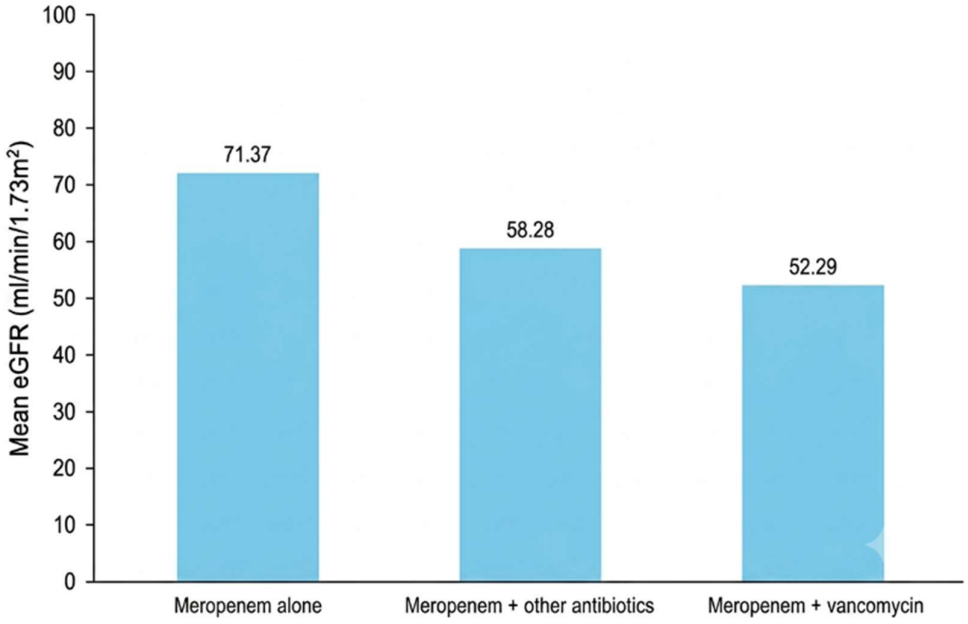

Figure 2: Comparison of eGFR (ml/min/1.73 m) across Antibiotic Groups

Kruskal–Wallis H = 7.692, p = 0.021.

Association Between Renal Impairment and Treatment Appropriateness

In this research, the association between the severity of renal impairment and treatment appropriateness is statistically significant across multiple factors, as shown in Table 3. There is a significant variation across renal function categories and the appropriateness of indication (χ^2 = 21.948, p < 0.001), with the lowest percentage among severely impaired patients (38.9%) and the highest among moderately impaired patients (87.5%).

Regarding the dose adjustment accuracy, there's a strong and significant correlation with renal function (χ^2 = 39.866, p < 0.001). The proportion of correct dosing declined progressively with deteriorating renal function, approaching to 0% in patients with severe renal damage.

In the same manner, the correctness of dosing frequency and renal impairment showed a strong correlation (χ^2 = 11.888, p = 0.008). There was a notable decline in moderate impairment (37.5%), while for mild impairment was the highest (78.6%).

Overall, these data show that there's no adjustment or individualization in dosing and frequency for renal impaired and particularly in severely damaged kidney patients.

Table 3: Association between Renal Impairment and Treatment Appropriateness

Renal Impairment	Indicated n (%)	Dose Correct n (%)	Frequency Correct n (%)
Normal	12 (50.0%)	18 (75.0%)	16 (66.7%)
Mild	22 (78.6%)	16 (57.1%)	22 (78.6%)
Moderate	28 (87.5%)	14 (43.8%)	12 (37.5%)
Severe	14 (38.9%)	0 (0.0%)	18 (50.0%)

Note:

- Indication: χ^2 = 21.948, p < 0.001, Cramer's V = 0.428
- Dose correctness: χ^2 = 39.866, p < 0.001, Cramer's V = 0.576
- Frequency correctness: χ^2 = 11.888, p = 0.008, Cramer's V = 0.315

Microbiological Culture and Treatment Appropriateness

Concerning the microbial culture performance and the appropriateness of receiving meropenem therapy, there's a statistically significant correlation (Fisher's

Exact test, p = 0.034). Merely 22.8% of patients who didn't undergo culture testing took meropenem as an appropriate therapy compared with 66.7% in the culture-positive patients, as shown in Figure 3.

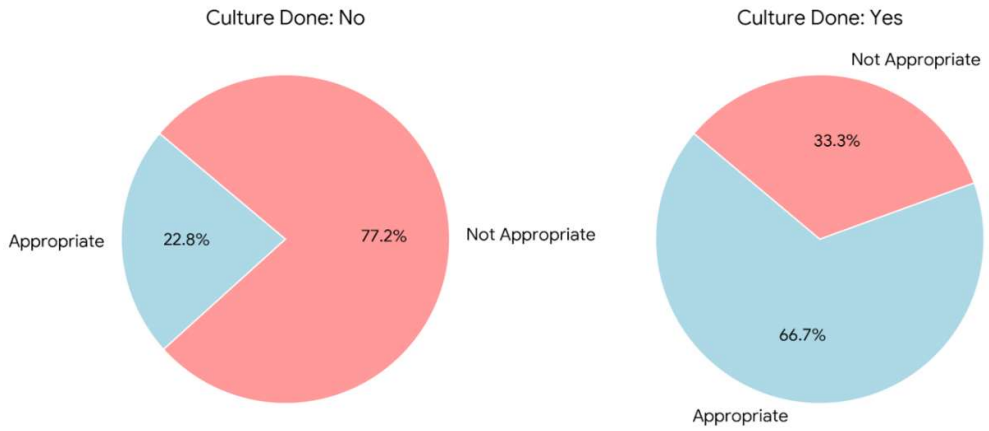

Figure 3: correlation between microbiological culture and treatment appropriateness

Fisher's Exact p = 0.034

DISCUSSION

In the current study on meropenem administration to ICU patients, a substantial incidence of medication errors was recognized, mainly related to indication, dose, dosing frequency, and renal adjustment, which all fall into the category of a clinical pharmacist's responsibility, where they can totally manage and avoid them from happening. (8,9,10)

Even though pharmacists were present in the unit, they were neither specialized nor trained in antimicrobial stewardship, nor did they have a board certificate in this field. The measurable clinical response to the therapy, combined with frequent errors in management, was evaluated to highlight the significant role and responsibility of clinical pharmacists with associations for resistance prevention, medication safety, and patient outcomes in optimizing meropenem usage. (11)

Meropenem therapy provided clinical benefit across most of the subgroups in this study, with a significant reduction in CRP and WBC after 48-hour treatment initiation. (12) However, patients who received meropenem non-consistent with guideline indications or inadequate dosing showed less pronounced effect compared to those who were appropriately prescribed in terms of indication and dosing regimens; the latter (appropriate group) presented a more marked decrease in inflammatory markers. These results indicate the urgent need for an active clinical pharmacist in reviewing meropenem prescriptions before and during initiation of the therapy in order to optimize and enhance the quality of patient outcomes.

In this study, serious safety issues were noted concerning the group of patients with renal impairment problems, either prescribed meropenem alone or combined with Vancomycin. There was a strong and statistically significant association between both dose and frequency of correctness with renal impairment. (13) With the decrease in renal function, there's a sharp fall in the proportion of dosing and correctness frequency, where in severe renal function reaching to 0%.

An additional point to consider is that eGFR ranks highest in patients receiving meropenem alone compared to meropenem combined with vancomycin or with other agents. (14) This shows a significant difference between antibiotic regimens as well as the risks of nephrotoxicity and under- or overdosing patterns. According to our data, there's a lack of eGFR monitoring, meropenem dose, frequency adjustment, and risks of nephrotoxicity due to combination therapies, all of which could be prevented by an active clinical pharmacist who could participate in the decision-making for optimizing the therapy. (15)

The low microbial culture testing rate is an extremely concerning aspect of this study, as there's a high reliance on empirical therapy without microbiological confirmation. Earlier research has proved a culture guided therapy reduces unnecessary

exposure to broad-spectrum antibiotics and hence better clinical outcomes, along with decreasing the antibiotic resistance, which aligns with the standard principles of antimicrobial stewardship. (16)

The culture group was very small; on the other hand, a significant portion of patients started meropenem without culture, which subjects them to antibiotic resistance, and this is associated strongly with a lower rate of appropriate therapy. Furthermore, despite the unclear indication and dosing errors of meropenem being common across the infection sites, especially in neurological and respiratory infections, suggesting broad trend towards empirical therapy that doesn't align with antimicrobial stewardship. (17) Consequently, a specialized clinical pharmacist could help long-term resistance prevention by taking a more active role in urging timely microbial culturing, analyzing results, and challenging unnecessary Meropenem prescriptions.

According to our observation in this study, the infusion strategies of individual patients are not being personalized to leverage their pharmacokinetic and pharmacodynamic differences, specifically in critically ill ICU patients with altered metabolism status, such as drug distribution and clearance. (18)

Almost all the patients have received meropenem with 30 min infusion rate, and very small number administered with prolonged 180 min whereas a clinical pharmacist could get involved in and select prolonged infusion for candidate patients with severe and life threatening infections, like intra-abdominal, pneumonia and some specific resistant bacteria, for preventing nephrotoxic affect in altered renal patients, continuous fever and those with no clinical improvement after 48 hours. This protocol is recommended and practiced by many researchers in this field. (19)

CONCLUSION

The findings in this observational study indicate that, despite the widespread use of meropenem in the ICU setting, yet they are widely used inappropriately, with repeated errors in indication, dose, dosing frequency, and renal adjustment. This is specifically obvious in patients with moderate to severe renal impairment, where their conditions are already critical due to their renal damage. Although meropenem is associated with early improvement of inflammatory markers, the low culture use and non-individualized infusion strategies point out additional shortcomings in antimicrobial stewardship. Overall, according to our data, the current meropenem prescribing pattern is suboptimal and needs to be revised by the management system and assign more active and trained clinical pharmacists in control of Antibiotic dispensing, especially meropenem in the ICU, in terms of renal dose adjustment, indication review, culture-guided, and individually optimized infusions to improve patient outcome and prevent antibiotic resistance.

RECOMMENDATIONS

1. Active clinical pharmacists must be implemented in the wards with clear daily responsibilities in terms of all meropenem prescriptions (indication, dose, frequency, infusion time, and duration).
2. Special renal adjustment protocol for meropenem prescription in patients with kidney disease and mandate a clinical pharmacist or senior physician's approval.
3. Mandate microbial culture before or shortly after starting meropenem. And reassess after 48-72 hours the need to continue or de-escalate in the patient.
4. Assign a team for inspecting antimicrobial stewardship and review the use of antibiotics in general and meropenem in specific.
5. Conducting a prospective interventional study to compare current data with another research, which includes a clinical pharmacist with a defined stewardship role to evaluate the impact on meropenem prescribing errors and patient outcomes.
6. Repeating the current research with a larger sample size and longer observational time.

Data Availability Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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No external funding was received for this study.

Conflicts of Interest

The authors declare that they have no competing interests.

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