

# Drug Utilization Evaluation of Meropenem in Surgical Patients in a Tertiary Trauma Care Hospital

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## ABSTRACT

Meropenem is considered as a potential drug for the treatment of Multi drug resistant gram –ve infections. The higher incidence of empirical prescription for this drug in hospitals will potentially increase the prevalence of resistance, making it an important candidate for execution of drug utilization evaluation (DUE). The primary objective of the study was to assess the Meropenem prescribed cases and evaluation of its appropriateness. Secondary objective was to find out the average cost spent solely for Meropenem pertaining to their respective specific and empirical therapies. A Prospective, questionnaire based study was conducted to evaluate the appropriate use of Meropenem. A total of 30 Meropenem prescribed cases were assessed in our study, which revealed 20% of empirical use and 80% of specific use, where 6.67% of prescription was inappropriate. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and the Enterobacteriaceae are the main MDR-GNB (multidrug resistant-gram negative bacteria) producing serious infections. There was an improvement of 66.67% after Meropenem use. According to APACHE II scoring, 50% of the patients had high risk for mortality in ICU, in which 57.17% of the patients got completely cured by the use of Meropenem. Considering the total ICU patients 78.57% of the patients got completely cured by the use of Meropenem. Total cost for the treatment with Meropenem expressed as mean  $\pm$  SD= Rs.19490.50 $\pm$ 14742.17. Mean cost of empirical treatment with Meropenem expressed

as mean  $\pm$  SD = Rs.14621.83  $\pm$  8239.88. Mean cost of specific treatment with Meropenem expressed as mean $\pm$ SD = Rs.20707.65  $\pm$  16167.01.

**Keywords:** Meropenem, Drug utilization evaluation, Multi drug Resistance, Empirical Therapy

## INTRODUCTION

Carbapenems are broad spectrum antimicrobial agents that have excellent activity against wide variety of bacteria. Epidemiological studies have shown a link between antibiotic use and resistance. The centers for disease control and prevention estimated 23,000 deaths per year in the USA due to infection by antibiotic resistant pathogens. Carbapenem resistant Enterobacteriaceae including *Klebsiella pneumoniae*, *Acinetobacter baumannii* are of increasing concern and have rapidly spread globally.<sup>[1]</sup>

Meropenem is considered as a potential drug for the treatment of multi drug resistant gram –ve infections like complicated intra-abdominal infections, skin and skin structure infections, nosocomial pneumonia, complicated urinary tract infections, due to the stability of these agents against the majority of beta lactamases and their high rate of permeation through bacterial outer membranes.<sup>[2]</sup> It

serves as a life saving drug in gravely ill patients, but recent reports regarding the resistance patterns of this drug is quite daunting.

The higher incidence of empirical prescription for this drug in hospitals will potentially increase the prevalence of resistance, making it an important candidate for execution of drug utilization evaluation (DUE). Drug utilization assessment is the marketing, distribution, prescription and use of drugs in society with special importance on the resulting medical, social and economic costs (WHO). The purpose of DUR is to ensure drugs are used appropriately, safely and effectively to improve patient health. [3] The primary objective of the study was to assess the Meropenem prescribed cases and evaluation of its appropriateness. Secondary objective was to find out the average cost spent solely for Meropenem pertaining to their respective specific and empirical therapies.

Consequently provide an overview of its use in hospital in order to promote the rational prescribing, dispensing and administration. Optimizing medication utilization has the potential to reduce the development of antimicrobial resistance and to lower overall healthcare costs by providing cost effective treatment.

## MATERIALS & METHODS

A Prospective, questionnaire based study was conducted during the period of

October to December of 2019, to evaluate the appropriate use of Meropenem in Ganga medical centre and hospital, Coimbatore. Cases were collected from the Plastic, Trauma, Spine, burns and Neurosurgery departments. The selection of the patients was according to their treatment with Meropenem, who were greater than 18 years of age.

Assessment was done to identify whether the drug have been approved by the physician and if there were any supportive microbiological evidences. All the 30 patients included in the study were followed up till the discharge. The clinical progress notes of physician were used to evaluate the clinical outcome of the patient during follow up days.

## RESULT

### MEROPENEM USAGE:

In our study it was found that the Meropenem use is confined to empirical (20%) and specific therapy (80%), in which the indications were surgical site infection (26.66%), complicated UTI (13.33%), bacterial meningitis (6.67%), sepsis (10%), complicated skin and skin structure infection (30%) and nosocomial pneumonia (6.67%). The irrational use of Meropenem constituted 6.67% (**Table No.1**). The Meropenem usage spanned from 1week (76.67%), 1-2 weeks (13.33%) and 2-3weeks (10%).

TABLE No. 1: INDICATION OF MEROPENEM

DISEASE INDICATION	TOTAL NUMBER	PERCENTAGE
Surgical site infection	8	26.66%
Complicated UTI	4	13.33%
Bacterial meningitis	2	6.67%
Sepsis	3	10%
Complicated skin and skin structure infection	9	30%
Nosocomial pneumonia	2	6.67%
Irrational use	2	6.67%
TOTAL	30	

### ASSESSMENT OF MEROPENEM THERAPY:

The dose regimen 1g IV q8h used by trauma, plastic, spine and neurosurgery unit, made a majority of 70%, and the cost per day was Rs. 2625/-.

The other regimens used were 500mg IV q8h (trauma, plastic, burns) costing Rs.1746.75/-per day, 2g IV q8h (plastic, neurosurgery) costing Rs.5250/- per day, 1g IV q12h (trauma) costing

Rs.875/- per day which constituted 6.67% each, and 1g IV q6h(trauma, plastic) costing Rs.3500/- per day, 500mg IV q12h (trauma) costing Rs.1164.5/- per day, 1g IV q12h (trauma) costing Rs.1750/- per day which constituted 3.33% each. (Table No. 2)

TABLE No.2 PRESCRIBED DOSE

DOSE REGIMEN	No. OF PATIENTS (n= 30)	COST OF THE REGIMEN PER DAY	UNIT
500 mg IV q8h	2	1746.75/-	Trauma /Plastic Burns
1g IV q8h	21	2625/-	Trauma Plastic Spine Neurosurgery
2g IV q8h	2	5250/-	Plastic/ Neurosurgery
1g IV QID	1	3500/-	Trauma / Plastic
500 mg IV q12h	1	1164.5/-	Trauma
1gm IVq24h	2	875/-	Trauma
1gm IV q12h	1	1750/-	Trauma
TOTAL	30		

Among the prescribed dose of Meropenem, 13.33% constituted inappropriate renal dosing. (Table No.3)

TABLE No. 3: INAPPROPRIATE RENAL DOSING

CREATININE CLEARANCE	RENAL DOSE	GIVEN DOSE	UNIT
10-25 ml/min	0.25-0.5gm IV q12h	1gm IV q8h	Spine
<10ml/min	0.25-0.5 gm IV q24h	0.5gm IV q8h	Trauma
26-50ml/min	0.5-1gm IV q12h	1gmIV q8h	Trauma
26-50ml/min	0.5-1gm IV q12h	1gm IV q8h	Trauma/Plastic

Among the total cases taken, cases of physician approved with supportive microbiological evidence made a majority of 33.33%, cases of physician approved without supportive microbiological evidence and clinically appropriate without supportive microbiological evidence made a total of 16.67% and the rest 30% were made by clinically appropriate with supportive microbiological evidence.

### **MICROBIOLOGY:**

The samples sent for the culture included urine (35.71%), wound swab (23.80%), pus and tracheal aspirate (9.52%), blood and tissue (7.14%), CSF (4.76%), and sputum (2.38%). The samples showed 73.33% gram -ve bacteria and 6.67% gram +ve bacteria 20% showed no growth. The gram-ve bacteria were majorly Klebsiella (40.63%), Pseudomonas (25%) and Acinetobacter species (18.75%). Among 73.33% of the cases, in which culture sensitivity test showed microbial growth, 27.27% showed resistance to Meropenem. 83.33% of the Meropenem resistance was shown by Acinetobacter species and the rest 16.64% was shown by Pseudomonas

species. The prescription pattern according to culture sensitivity data was 63.33% and not accordingly was 36.67%.

### **TREATMENT OUTCOME:**

Among the total patients, a majority of 40% showed response within 48-72 hours after Meropenem initiation, 23.33% showed response <48 hours, 30% after 72 hours of exposure and 6.67% showed no response. The vitals (Blood pressure, Temperature, PR, HR, RR) of the patients have been observed before and after the Meropenem use and a complete improvement of 63.33% was achieved. The mean abnormal values of WBC (15084±2683.81), Procalcitonin (25.66±28.36), ESR (89±59.92), and C-reactive protein (136.08± 79.08) was taken as the hematological parameters of observation. There was an improvement of 66.67% after Meropenem use. According to APACHE II scoring, 50% of the patients had high risk for mortality in ICU, in which 57.17% of the patients got completely cured by the use of Meropenem. Considering the total ICU patients 78.57% of the patients got completely cured by the use of Meropenem.

The treatment success was 90% and 10% resulted in death.

### **COST CONSIDERATIONS:**

The mean length of hospital stay among total patients was found to be 27.26 ±17.56, mean length of ICU stay was 10.86 ± 5.95. Average length of stay of the total sample size was 27.26 days, average length of stay of patients in ICU was 15.32 days. Total cost for the treatment with Meropenem expressed as mean ± SD = Rs.19490.50 ± 14742.17. Mean cost of empirical treatment with Meropenem expressed as mean ± SD = Rs.14621.83 ± 8239.88. Mean cost of specific treatment with Meropenem expressed as mean ± SD = Rs.20707.65 ± 16167.01.

### **DISCUSSION**

The Carbapenems are a group of broad spectrum beta-lactam antibiotics, which in many cases are the last effective defense against infections, caused by multi drug resistant bacteria. Meropenem is one among them which is indicated to treat complicated skin/skin structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), community acquired pneumonia (CAP), complicated UTIs, Bacterial meningitis and febrile neutropenia.<sup>[4]</sup>

A total of 30 Meropenem prescribed cases were assessed in our study, which revealed 20% of empirical use and 80% of specific use, where 6.67% of prescription was inappropriate prescription pertaining to the condition of the patient. Whereas the appropriate uses includes empiric treatment of severe nosocomial infections in critically ill patients or in ICU, Failure of first line antibiotics for gram negative bacterial infections, Directed treatment according to the results of culture and susceptibility testing, chronic multi drug resistant pseudomonal infections.<sup>[5]</sup> Those 6.67% cases had no signs of infection and totally irrational with respect to which the antibiotic is indicated.

Meropenem is mainly excreted through the renal route. Renal function is a vital determinant for achieving effective antibiotic exposure<sup>[6]</sup>. For patients with normal renal function, Meropenem is usually administered every 8 hrs. In end-stage chronic renal failure, the half-life of Meropenem is prolonged to 7 to 10 hrs, so one dose every 24 hr is considered appropriate and an additional dose is recommended after dialysis<sup>[7]</sup>. Our study consists of 13.33% of inappropriate renal dosing which is a suggestive of redundant and devastating accumulation of Meropenem metabolites in the body, and corrective measures were taken by the clinical pharmacist as soon as possible.

On assessment of the improvement in the clinical signs and symptoms of the patients undergone with empirical and specific therapies, The vitals (Blood pressure, Temperature, PR, HR, RR) have been observed before and after the Meropenem use and a complete improvement of 63.33% was achieved. Clinical data of studies suggests a high rate of clinical efficacy with a low frequency of adverse effects. The severity of disease in ICU admitted surgical patients were assessed using the APACHE II scoring and the patients who came under highest hospital mortality score were expired.

Usually patients requiring prolonged courses of Carbapenem antibiotics such as Meropenem, often have incessant comorbidities or a predominance of complex infections involving *P.aeruginosa* and resistant Enterobacteriaceae, and concomitant administration of antibiotics. These are main factors contributing towards clinical failure and severe adverse affects. 10% of death cases in the study is an example of such a situation where the patients were directed to Multi-Organ dysfunction following Sepsis.<sup>[8]</sup>

*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and the Enterobacteriaceae are the main MDR-GNB producing serious infections<sup>[9-10]</sup>. MDR *A.baumannii* frequently produces

nosocomial infections and pestilent situations in ICUs all over the world. Pseudomonas also has similar trajectory. Our study is an evidence of such a case was 40.63% culture tests of various samples grew Klebsiella species, 25% pseudomonas and 18.75% Acinetobacter baumannii. Out of all the prescriptions 63.33% were according to the culture sensitivity data, which means the optimal choices for the specific treatment of severe infections caused by K. pneumoniae, A.baumannii and Pseudomonas species was Meropenem<sup>[11]</sup>.

Duration of therapy may be prolonged in certain aforementioned conditions including empirical prescriptions, whereby certain treatment protracts consequently, burdening the treatment expenses<sup>[12]</sup>. The length of stay of patients in hospital expressed as Mean  $\pm$  SD is 27.26  $\pm$  17.56. Mean cost of empirical treatment with Meropenem expressed as mean  $\pm$  SD = Rs.14621.83  $\pm$  8239.88. This means the 20% of empirically treated patients have afforded extra expenses.

## CONCLUSION

The inappropriate use of Meropenem is associated with the detrimental effects, including emanation of antibiotic resistance. Our study which also out looked the rationality and further evaluation on the appropriate use of Meropenem, frames an inference that it is necessary to take actions like maintaining a guidelines or checklist to improve prescribing habit in order to reduce the unnecessary usage of antibiotic; therefore curbing the resistance and providing economically reliable treatment is a major public health priority<sup>[13-14]</sup>. Further studies regarding the pharmacokinetic and Pharmacodynamics of the drug may result in more precise and accurate data regarding the dosage regimen and adjustment of the therapy.

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