

**COST-MINIMIZATION ANALYSIS OF MEROPENEM VERSUS  
IMIPENEM/CILASTATIN IN MODERATE TO SEVERE INFECTIONS  
AT A TERTIARY CARE GOVERNMENT TEACHING HOSPITAL – A  
PHARMACOECONOMIC AND EPIDEMIOLOGICAL STUDY**

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**ABSTRACT**

**Background:** Antibiotics are playing very crucial role in every health care system. According to WHO 2009 statistics almost 50% of the patients in India (Karnataka) are using antibiotics regularly and repeatedly over a period of life time<sup>1</sup>. The updated Pharmacoeconomic and epidemiological studies on antibiotics are scarce in India. **Aim:** The main aim of this study is to compare the costs of imipenem/cilastatin and meropenem in management of moderate to severe infections in different diagnosed patients. These both drugs are belonged to the carbapenem class of drugs, sharing a similar spectrum of activity. **Methodology:** It is a retrospective longitudinal (Cohort) study including 90 patients with moderate to severe infections managed with Imipenem/Cilastin and Meropenem were observed simultaneously in the period of September 2014 to December 2014.

The data was collected from the medical records, following by physician notes and through counselling few patients who are on regular follow up. Cost Minimization Analysis was used to find out the best economic drug among them based on the ROA (Route of Administration), Frequency, Dose, length of hospitalization and other aspects were well considered. Patients with >18 yrs age group were considered in this study. Paediatrics population were excluded as the documentation was incomplete. Patients who are diagnosed with moderate to severe infections include Urinary Tract Infections, Abdominal Infections, Sepsis, and Respiratory tract infections, Skin Infections, Hospital Acquired Infections, who were prescribed with imipenem/cilastatin 500 mg q6 hr. i.v or meropenem 1gram q8 hr. Were included in the study.

As the study area is in a government setup only medication cost was included in accordance with *payer perspective*. **Results:** The total number of cases attended to General Medicine Department from September 2014 to December 2014 is 348. The total number of moderate to severe infection cases attended to General Medicine Department in a tertiary care hospital in 4 months of time period was 151, among them 90 patients were taken as subjects for demonstration of analysis of meropenem versus imipenem/cilastatin. Most of the cases were between 21 to 40 years of age group, resides in the rural areas. There is a significant difference in the mean total daily costs between the two drugs [statistically analysed report] is (4356 of imipenem/cilastatin, 3240 for meropenem). The cost of administration set, also rocketed the daily cost of imipenem/Cilastin. There is no documented ADR (Adverse Drug Reaction) reporting forms in these cases. **Conclusion:** The study has shown that the mean total cost of meropenem 1g q8 hr. is lower than the cost of imipenem/Cilastin at a dose of 500mg q6hr. This study partially states that the cost of drugs in managing the moderate to severe infections are crucial elements of the overall costs. They also to be considered along with non-medical costs and intangible cost in case of policy making.

**KEYWORDS:** Imipenem/cilastatin, Meropenem, Moderate to severe infections, Pharmacoeconomics, pharmacoepidemiology, payer perspective.

## INTRODUCTION

The true cost of health care is totally depends on the consumption of society's resource. Under a traditional medical system, hospital costs (mainly medication costs, medical indirect costs) are mostly paid by the payers or health insurance persons.<sup>[3]</sup> Antibiotics are the essential medicine in a health care system. In worldwide, they stand in the third place in case of mostly using drugs. The cost burden of the antibiotics is needed to be measured in budget preparation. Carbapenems play a critically important role in our antibiotic armamentarium. Of the many hundreds of different  $\beta$ -lactams, carbapenem possess the broadest spectrum of activity and greatest potency against both Gram-positive and Gram-negative bacteria. As a result, they are often used as "antibiotics of last resort" when patients with infections become gravely ill.

The hospital formulary lists two carbapenems: the fixed dose combination of imipenem/cilastatin and usual dose of meropenem. These two drugs sharing similar spectrum of activity and the unit cost is almost similar, but when we considering the frequency of the drugs the imipenem/cilastatin is expensive. There are conflicting reviews with regard to the

relative cost-effectiveness of these two drugs. It would be appropriate, therefore, to test the economic impact of the main factors influencing hospital costs by basing on pharmacoeconomic principles. In this case the CMA (Cost Minimization Analysis) could provide an estimate of the economic impact of these therapeutically equipotent drugs using in India.

The aim of our study is to contribute to the rational selection of medicines, in order to achieve good therapeutic effects and better patient outcomes, by focusing on cost-effectiveness of the drugs.

### **Pharmacoeconomic analysis**

It identifies the cost and consequences of alternative medicines therapy in order to make the best possible decision, while ensuring the maximum benefit and efficiency of budgets.<sup>[7]</sup>

In this study CMA (Cost Minimization Analysis) approach is selected. In this, only the input, i.e. the cost, is considered. The option that has the least cost is selected, e.g. if a hospital decides to introduce compulsory prescribing of generic names of drugs instead of their brand names, then the pharmacoeconomic evaluation of this would be done by CMA.<sup>[5]</sup> However, the application of generic prescribing in an Indian setting would require more pilot studies at the level of primary healthcare providers, general physicians, policy-makers and regulatory authorities.

### **Pharmacology**

Carbapenem are belongs to  $\beta$ -lactams drugs of classification. Among the  $\beta$ -lactams currently available, carbapenem are unique because they are relatively resistant to hydrolysis by most  $\beta$ -lactamases, in some cases act as “slow substrates” or inhibitors of  $\beta$ -lactamases, and still target penicillin binding proteins. This “value-added feature” of inhibiting  $\beta$ -lactamases serves as a major rationale for expansion of this class of  $\beta$ -lactams.<sup>[4]</sup> The combination of imipenem and cilastatin fixed dose of 500mg q 6hr was well tolerated and safe.<sup>[8]</sup> The FDA approved meropenem dosage for mild to moderate infections varies from 500mg to 1g for every six to eight hours. The dose should be adjusted in case of renal impairment patients and when the Cr.Cl (creatinine clearance)  $\geq 5\text{ml/min/1.73 m}^2$  the drug should not be administered. The doses need to be calculated based on the weight of the patient too.<sup>[9]</sup>

Literature review and appraised in order to show the confirmation of therapeutic equivalency of both the drugs:

Total 26 studies were retrieved by using the various source like Cochrane Library, Medline database, PubMed, wiley library, Google scholar and other resources are also used. However mostly focused on the systematic reviews, meta-analyses, pharmacoeconomic studies, pharmacoepidemiology studies and other relevant studies were also retrieved. Some of the supported articles were enlisted in given table.

Some of the studies supported the 1.5g/day of meropenem is as effective as 2g/day of Imipenem and Cilastatin and some articles supported the similar frequency of these drugs are clinically effective.

**Table: Summary of literature appraisal**

S.no	Clinical assessment	Supported articles
1.	Clinical equivalency of Imipenem/cilastatin versus Meropenem in case of SEPSIS	(Jamal Ahmad Wadi M.D1* Fadi Shaqlose Pharm D et.al., Imipenem/cilastatin versus Meropenem on Fever Defervescence in Septic Febrile Patient: A Comparative Prospective Study;(2012) ; iajaa; Vol. 2 No. 2:3 doi: 10.3823/712;[ iMed Pub]
2.	Clinical equivalency of IC versus Meropenem in case of UTI	C.E.Cox, W.J.Holloway et.al., (1995); A multicenter comparative study of meropenem and imipenem/cilastatin in the treatment of complicated UTI in hospitalized patients; clin.infect.dis.,21(1) (1995),pp 86-92.
3.	Clinical equivalency of IC versus Meropenem in case of moderate to severe IAI	Matthew N. Lowe, Harriet M. Lamb(2012) Meropenem; September 2000, Volume 60, Issue 3, pp 619-646 [Springer]
4.	Clinical equivalency of IC versus Meropenem in case of moderate to severe Respiratory tract Infection	H.Xiao, B.Cao,et.al; A meta-analysis of the efficacy and safety of meropenem and imipenem in the treatment of moderate or severe pulmonary infections; Chin.j.Infect.Cheother., 10 (4)(2010), pp.264-269
5.	Clinical equivalency IC 500 mg q6 h and Meropenem 1 gram q8 h	George G Zhanel, PharmD PhD; et.al; Imipenem and meropenem: Comparison of in vitro activity, pharmacokinetics, clinical trials and adverse effects; Can J Infect Dis. 1998 Jul-Aug; 9(4): 215-228.[PMC]

IAI: Intra-abdominal infections, IC : Imipenem/ Cilastatin

## ECONOMIC EVALUATION OF DIFFERENT BRANDED DRUGS OF MEROPENEM AND IMPENEM/CILASTATIN

With the help of the clinical pharmacist, different branded drugs that are been selling in various community pharmacies are documented and they were presented depending on their costs in ascending manner. These are available in both generic and branded forms in 14 drug stores. At sure this data will be helpful to the physician, pharmacist and patient in choosing the desire drug of particular brand in their budget.

**Table: Various available meropenem drug brands and their costs<sup>[2]</sup>**

S.NO	Name	Type	Manufacturer name	Unit	Price	Active ingredients
1.	Synmero	injection	Sanify Health care Pvt.Ltd.	1 Vial	139.90	MEROPENEM-1000 mg
2.	Meropenem	injection	Jan Aushadhi	1 vial	416.00	MEROPENEM-1000 mg
3.	Menoree	injection	Research Medicure Pvt.Ltd.	1 vial	498.00	MEROPENEM-1000 mg
4.	Mexico	injection	Reco Drugs	1 vial	490.00	MEROPENEM-1000 mg
5.	Ronem	injection	Venus Remedies	1 vial	1080.00	MEROPENEM 1000 mg
6.	Qopenem	injection	Quick Heal Life Sciences	1 vial	1095.00	MEROPENEM 1000 mg
7.	Medipanam	Injection	Medihealth Lifesciences Pvt.Ltd.	1 vial	1570.00	MEROPENEM 1000 mg

**Table: Available Imipenem/Cilastatin brands through cost comparison.**

S.NO	Name	Type	Manufacturer name	Unit	Price	Active ingredients
1.	Imastat	Injection	Ruan lifesciences	1 vial	830.00	Imipenem-500 mg Cilastatin- 500 mg
2.	Cilaxure	Injection	Nexure Life Sciences	1 vial	849.00	Imipenem-500 mg Cilastatin- 500 mg
3.	Iminem	Injection	United Biotech(P)Ltd.	1 vial	850.00	Imipenem-500 mg Cilastatin- 500 mg
4.	Cilanem	Injection	Ranbaxy Laboratories, Ltd.	1 vial	1089.00	Imipenem-500 mg Cilastatin- 500 mg
5.	Imitop	Injection	Sanat products Ltd.	1 vial	1099.00	Imipenem-500 mg Cilastatin- 500 mg
6.	Cilaspene	Injection	Sanjivani Parentral Ltd.	1 vial	1100.00	Imipenem-500 mg Cilastatin- 500 mg
7.	Lastinem	Injection	Venus Remedies Ltd.	1 vial	1113.00	Imipenem-500 mg Cilastatin- 500 mg

### Methodology

This study is a retrospective single centre cohort study based on cost minimization analysis, in order to establish pharmaco-economic culture in government sectors, by comparing the costs of equipotent medicines used in managing different diseases therapeutically. In this study the cost minimization analysis was conducted in between imipenem/Cilastatin and Meropenem in moderate to severe infections, which was conducted at a Government hospital, in the period of September 2014 to December 2014, all patients receiving IC 500 mg every six hours and MEM 1 g every eight hours for moderate to severe infection were included in the study. The study set out to capture 90 patient files with 45 patients in each arm, based on the estimated

census of patients treated with these medicines in a calendar year. The perspective of the economic evaluation was that of the provider or payer, in this case the Ministry of health; India that provides health-care to eligible patients.

The inclusion criteria consider the adult patients of age  $\geq 18$  years old, diagnosed with moderate to severe infection, including sepsis, IAI, respiratory tract infections, UTI and Skin infections and who were prescribed with IC 500 mg every six hours intravenously (2 g per day); patients diagnosed with moderate to severe infection, including SSI, sepsis, IAI, respiratory tract infections, UTI and skin infections and who were prescribed with MEM 1 g every eight hours intravenously (3 g per day) were included in the study.

The exclusion criteria includes, those that were pregnant; with known or suspected meningitis; diagnosed with microorganisms resistant to IC or MEM; Renal, and hepatic impairment patients and patients ( $< 18$  years old) are excluded in this study.

The data of patient's demographic details and therapeutic details, drug management and laboratory reports were collected from the hospital records, patient's case sheets, physician notes and follow-up charts. The case sheets consists of the detailed notes on the patients demographics, past medical, medication history, laboratory data and treatment chart and microbiological tests. The follow-up charts show the complete recovery of the patient and their drug compliance. Doubts are clarified by referring the physician's notes. There is no recorded reports of the ADE (Adverse Drug Events) and treatment failure cases among selected 90 patients. The data on the dose, dosage form, frequency, length of hospitalization and presence of antibiotics were particularly recorded.

### **Statistical analysis and costing calculation**

The primary objective of the study was to compare the costs of management of moderate to severe infections in patients treated with IC and MEM. Descriptive statistics were presented as mean  $\pm$  standard deviation for all continuous variables (e.g., age) while number (%) were reported for all categorical variables (e.g., gender). The mean total daily costs was calculates my using (Microsoft excel graph sheet) and student-t test was applied to get the statistically appropriate results. A two sided  $p$ -value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using statistical software.

As the study place is a Government sector only the cost of the medicines were considered and remaining services are free to the patients. The intangible cost and direct non-medical costs were not included in the study.

## RESULTS

Almost 100 patients were observed and 90 patients are considered in to the study, 45 on each arm who are diagnosed with moderate to severe infections of different origins and treated with IC or meropenem were considered in this study. Total number of patients are (N=90), in these 42 are male of (46.67%) and 48 are female of (53.33%). Patients with age group of 21-40 includes 55 members which shows highest percentage distribution of 61% and least were founded in between 61-80 years and it was 18%, there are no patients in both age extremities.

**Table: Age wise distribution of subjects**

S.No	AGE	Number of patients (N=90)	Percentage of distribution
1.	0-20	0	0%
2.	21-40	55	61%
3.	41-60	19	21%
4.	61-80	16	18%
5.	81-100	0	0%

**Table: Sex wise distribution of subjects**

S.No	SEX	Total Number of patients (N=90)	Percentage of distribution
1.	Male	42	46.67
2.	Female	48	53.33%

**Table: Regional wise distribution of data**

S.No.	Patients disease	Guntur	Krishna	Prakasham	Other Dist.	Total Number
1.	Cases with sepsis	09 (21.95%)	07 (26.92%)	03 (21.42%)	02 (22.22%)	21(23.33%)
2.	Cases with UTI	08 (19.51%)	06 (23%)	04 (28.57%)	01 (11.11%)	19(21.11%)
3.	Cases with IAI.	07 (17%)	03 (11.53%)	01 (7.14%)	00 (0%)	11(12.22%)
4.	Cases with LRTI	13 (31.7%)	07 (7.77%)	04 (28.57%)	06 (66.66%)	30(33.33%)
5.	Cases with skin infections	04 (9.75%)	03 (11.53%)	02 (14.28%)	00 (0%)	09(10%)
	Total Number	41 (45.56%)	26 (28.89%)	14 (15.56%)	09(10%)	90(100%)

\*UTI- Urinary Tract Infections, IAI- Intra Abdominal Infections, LRTI-Lower Respiratory Tract Infections.

Most of the cases were LRTIs and followed by sepsis and UTI, majorly UTI are found in the female patients. Among three districts the census was more with Guntur followed by Krishna, Prakasam and other districts. Above table enlists the percentage regional wise distribution of data.

### Demographic characteristics

There were no significant differences in demographic details of both group and it was summarized in given table.

**Table: Demographic characteristics**

S.No	Characteristic	Imipenem/cilastatin(n=45)	Meropenem(n=45)	P Value
1.	AGE (Yr.)	60.64 ± 19.04	52.11 ± 21.28	0.624
2.	WEIGHT (Kg.)	71.21 ± 15.71	68.60 ± 21.62	0.516

The hospitalization cost, visiting cost, both direct and indirect medical costs, non-medical costs were nil significant, as the study place was a government sector, all services to the patient were free of cost. The cost of medicines were obtained from the finance section of central drug store and compared with the least economic brand drugs that are available in community pharmacies.

In this study there is a comparison of the mean daily costs using independent sample – *T* tests demonstrated a significant difference in terms of mean daily cost. A significant lower medicine acquisition vial cost was observed for Meropenem (INR 1080, 95% CI 989.06–1263.20) compared to Imipenem/cilastatin (INR 1089, 95% CI 986.12–1120.84) ( $p < 0.001$ ). As there is a lower variation in the vial cost but the frequency of dose administration is rocketing the cost of imipenem/cilastatin. As Imipenem/cilastatin 500 mg every six hours and Meropenem 1 g every eight hours respectively. The total length of hospitalization was recorded in order to calculate the total budget of these two antibiotics.

### DISCUSSION

Some of the evidence based studies states that the imipenem/cilastatin was accompanied by lower costs per patient than meropenem.

The most relevant variables in the study of the efficiency of the treatment of intra-abdominal infections were, in conditions of equivalent effectiveness, days of hospitalization (and associated costs) and majorly drug price.<sup>[11]</sup>

In case of presenting the epidemiological data, it's a small size of sample, calculated and presented the data in regional wise, it helps in calculating the cost of travelling and other direct non-medical costs can be calculated by basing on the data.

Some of the evidence based studies states that 1.5 g/day of imipenem/cilastatin is equivalent to 3.0 g/day meropenem in clinical and bacteriological outcome rather than 2g/day of imipenem/cilastatin is equivalent to 3.0 g/day meropenem in treating moderate to severe infections.<sup>[12]</sup>

This study was not without limitations. It was a retrospective single-cohort study that reflected the practices of a tertiary care teaching hospital. Although a census approach over a calendar year was used, the sample size was small.

Despite of these limitations, our study has provided insight into the factors influencing hospital budgets at our institution.

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#### **CONCLUSION**

It is a retrospective cohort study that reveals the burden of two drugs on payer (Patient, Government, or Health policy) during their hospitalization. Being wise in selection of type of medicine and their brands decreases the burden of economy on the payers. Although the unit vial costs of meropenem and imipenem/cilastatin are almost similar, the mean daily cost of those drugs vary at high. As these drugs are need to be administered 10-15 days of duration, they will become hard nut in the budget preparation. The study also focuses out the importance of costs of drug in government sectors and their role in preparation of budget. Nonetheless, this study supports the prescribing of meropenem in treating the moderate to severe infections. It is rationale and economically supportive.

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