ejpmr, 2016,3(6), 454-462

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COST-EFFECTIVENESS OF CEFTRIAXONE-SULBACTAM IN TREATMENT OF NOSOCOMIAL INFECTIONS USING PROBABILISTIC SENSITIVITY ANALYSIS

Vishnu Dutt Sharma[a], Manu Chaudhary[a] and Manish Taneja[a*]

Venus Medicine Research Centre, Hill Top Estate, Bhatoli Kalan, H.P., India[a].

***Corresponding Author: Vishnu Dutt Sharma and Manish Taneja**

Venus Medicine Research Centre, Hill Top Estate, Bhatoli Kalan, H.P., India.

Article Received on 15/04/2016 **Article Revised on 04/05/2016** **Article Accepted on 25/05/2016**

ABSTRACT

Increasing prevalence of carbapenem resistance in gram negative bacteria due to excessive and indiscriminate use of carbapenems has forced the medical fraternity to look for better alternatives. One promising solution is to use pharmacodynamically synergistic drugs combination against the resistant pathogen. Recently, a fixed dose combination of ceftriaxone/sulbactam (2/1) (marketed as Elores®) has shown promising response against antibacterial resistance. However, the economic evaluation of Elores in comparison with carbapenem class of drug was not done so far. Therefore, the objective of the present study was to evaluate the cost-effectiveness of Elores and meropenem against hospital acquired infections (HAIs). A retrospective study on patients receiving either Elores or meropenem with/without colistin in management of HAIs was utilized for the cost effective analysis (CEA) study using 'decision table" as an analytical model. Cost of therapy evaluation included both direct and indirect costs. Effectiveness measures were estimated from drug's efficacy, adherence tendencies and tolerability in the model. The cost effectiveness ratio (CER) was computed, where Elores treatment was more cost-effective than meropenem treated approach with CER of INR 1132 (USD $ 17.4) per unit of effectiveness measures. The probabilistic sensitivity analysis was then performed to improve the model predictions, and to reduce the uncertainty in the model parameters. In base-case analysis, Elores was superior with an incremental-CER (ICER) of INR 27 at willingness-to-pay (WTP) of INR 200. The model was robust to variations in model input parameters. The study advocated Elores as a cost-effective use of resources and as a carbapenem sparer drug in the management of HAIs.

KEYWORDS: Cost Effectiveness Analysis, Antibacterial Therapy, Decision tree analysis, Probabilistic sensitivity analysis.

INTRODUCTION

Increased prevalence of bacterial infections coupled with rising antibacterial resistance has lead scientific community to hunt for newer alternatives. The situation becomes even worse with declined interest of pharmaceutical company due to exorbitant cost of drug development and shorter lifespan of antibiotics. The cost implications of antibacterial resistance are rising consistently and imposing serious challenge to developing countries due to their weak institutional and individual capabilities to manage such resistant infections.[1] The alarming situation can only be dealt by replenishing the dried pipeline of drug development with newer, efficacious and cost-effective antibiotics.

Hospital acquired or nosocomial infections (HAIs) are one of the most common infections in developing countries, due to their poor environmental sanitations and governance in health systems.[2] Lower respiratory tract infections, urinary tract infections and intra-abdominal infections are amongst the most prevalent HAIs, occurring from bacterial pathogens such as *E. coli*, *P. aeruginosa*, *P. mirabilis*, *K. pneumoniae*, *Enterobacter spp*., just to name a few. [3] Currently, carbapenems and beta-lactams drugs are frequently prescribed for the management of HAI; however, resistance cases are being frequently reported, which is making both classes gradually losing its clinical value. [4, 5] The hope of a magic potion seems to be illusional; and thus trying out a smarter approach of combining pharmacodynamically synergistic drugs remains justified.[6, 7] One such attempt was made by combining beta-lactam drug (i.e. ceftriaxone) with beta-lactamase inhibitor (sulbactam) in fixed ratio of 2/1 (w/w) (Brand name-Elores®). Elores has been reported to have proven efficacy in wide range of infections.[8-11]

Special mention must be made of the recent work done by Sharma et al. on dose optimization of Elores to enhance its anti-bacterial effect in different age groups using pharmacokinetic and pharmacodynamic modelling tools.[9-11] However, efficacy of drug is not the only

requirement for a new formulation to be successful in market especially of developing countries such as India; the formulation has to be cost-effective as compared to other commercially available formulations. Therefore, cost effectiveness of Elores was needed to evaluate its standing against commercial available carbapenem drugs.

The objective of the present study was to evaluate the cost-effectiveness of Elores in comparison with meropenem; and thus, to explore its potential as a carbapenem sparer drug from both aspect i.e. cost and efficacy. The study has utilized the clinical data of patients diagnosed with HAI in an Indian hospital.[12] The first part of the study was focused on evaluating cost-effectiveness of two approaches i.e. meropenem-treatment and Elores-treatment employed in Bhatia et al.'s retrospective study using decision table analysis (Figure 1).[12] The second part of the study extrapolates the findings through probability sensitivity analysis (PSA) to account for the uncertainties in the model parameters, and to provide more confidence in the economic evaluation of meropenem and Elores treatment against HAIs in India (Figure 2).

MATERIAL AND METHOD

Study design

The study had employed the data from the retrospective study of evaluating the clinical efficacy of Elores and meropenem in the treatment of HAI.[12] Briefly, it was conducted at Asian institute of medical sciences, Faridabad. Patients showing sensitivity towards new Elores or meropenem were considered eligible for the study. All the necessary lab investigations like sputum, broncho-alveolar lavage (BAL), endotracheal (ET) secretions, urine and blood culture and sensitivity reports, hematology, biochemistry and other relevant investigations were carried out at baseline and end of treatment. Patients were assigned to receive either meropenem (1.0 g, every 8 h) (Group 1 or G1) or Elores (1.5 g or 3.0 g, every 12 h) (Group 2 or G2) through intravenous administration. For those patients who were more severe or failed to respond to Elores, colistin with a loading dose of 9 MIU followed by BD doses of 4.5 MIU were used along with previous antibiotic. The clinical efficacy of the therapy was evaluated and classified as cured (resolution of clinical signs and symptoms or improvement not requiring further antibacterial therapy), or failure (persistence of clinical signs and symptoms or worsening in signs and symptoms that required alternative antimicrobial therapy after 72 h of treatment).

Determination of costs

Direct (cost of drugs, diagnosis/monitoring, personnel and transportation) and indirect (loss of productivity) costs were included in cost of therapy evaluation. Antibacterial cost was the maximum retail price of drug available in India market. The defined daily dose of the Elores and meropenem was taken from their respective product monographs.[8, 13] The cost for diagnostic (microscopy, culture and sensitivity) was set to INR 2860. For personnel cost, the ICU cost of Rockland hospital, Delhi was used i.e. INR 7500 which collectively includes cost incurred as result of completion of tasks such as consultation, dispensing and drug administration, and salaries of health professionals. Transportation cost was calculated as the average transport cost per return trip to the hospital by the patients, which was set to be INR 500.

The indirect cost due to loss in productivity as a result of hospital attendance by the patients was determined using the human capital method.[14] This was calculated based on time spent in the hospital and loss in earnings on a 40-hour, 5 day working week. The minimum daily salary i.e. INR 467 per day was used based on the minimum hourly wages of workers in India. An average family daily loss and loss in productivity (indirect cost) per hour was also added to indirect cost, which also includes time spent for diagnostic testing, treatment and transportation. Discounting of cost and adjustment for inflation was not carried out as all the costs occur within one year of analysis.

Determination of Effectiveness

In the analytical model, the criteria considered in the effectiveness rating were degree of efficacy, adherence tendency and humanistic outcomes.[15] The values of the degree of efficacy; a proxy measurement of cure rates for the Elores and meropenem were obtained from the results of antibacterial susceptibility testing of 95 isolates of *E.coli*, *Klebsiella sp*., *Pseudomonas sp*. and *Acenetobacter* species.[12] Intermediately sensitive and resistant clinical isolates were excluded. Focusing on adherence tendency, the frequency of dosing with once daily administration was allotted 100% adherence tendency while twice daily, and three times daily administration were allotted 50.0%, and 33.3% adherence tendency respectively.[15, 16] Product monographs of the Elores and meropenem were reviewed for incidences (rate) of adverse drug reactions for these antibacterial agents.[8, 13] Humanistic outcomes were measured as tolerability prorated from literature reported degree of adverse drug reactions events, risk of infection and pains from drug administration. For each of the criterion in the rating, weight was then assigned based on consensus amongst the authors. The degree of efficacy, adherence tendency, and tolerability were assigned weights of 0.5, 0.2 and 0.3, respectively.[15] The degree of effectiveness of each antibacterial agent was the sum total of the criterion rating which was calculated as the product of criterion value and assigned weight.[17] The cost effectiveness ratio (CEA) was then determined from societal perspectives by dividing the total cost of therapy by degree of effectiveness obtained from decision analysis.

Decision Tree model and inputs

The costs and outcomes of the Elores and meropenem strategies (without any colistin addition) were further analysed using a decision tree model. The model was constructed using a cohort simulation approach.[18,19] The decision tree was built in TreeAge Pro 2015 (TreeAge Software, Inc, Williamstown, MA) (Fig 1). All 65 patients were divided into categories i.e. Elores treatment or meropenem treatment. As shown in figure 2, the model had two branches at the decision node, i.e. Elores treatment and meropenem treatment. Each chance node was then bifurcated into two transition nodes i.e. cure and failure. Cost and effectiveness rating were assigned to all outcomes. Model inputs were (i) transition probabilities for each treatment, (ii) cost, and (iii) effectiveness of both treatments (Table 3). Beta distribution was assigned to transition probabilities of both treatment, and normal distribution was employed in cost estimates of meropenem; whereas Elores cost estimates were fixed for the CEA to improve the model parameter stability.

Probabilistic sensitivity analysis (PSA)

Monte Carlo simulations were performed (N=1000 iterations) to simultaneously account for the various uncertainties in the model parameters (Table 3), including transition probabilities at each cycle. In each iterations, this method randomly drew a value from the distribution in Table 3. For each estimates, the cost, effectiveness and the uncertainty around these estimates (expressed as 90% confidence intervals) were estimated.[20] The ICER analysis of the Elores and meropenem was carried out using equation-1.[21] The preferred strategy was determined by comparing the ICER to what decision makers are willing to pay for an additional effectiveness. To be considered cost-effective in the present study, willingness-to-pay (WTP) was set to INR 200 per unit increase in effectiveness. Cost effectiveness acceptability curve (CEAC) was constructed to estimate the joint impact of uncertainty in model parameter, and potential variability in the decision maker's WTP threshold for considering a treatment cost effective.[18,19] This method uses the net benefit (NB) framework, defined in equation-2:

$$. ICER = \frac{Cost\_1 - Cost\_2}{Effectiveness\_1 - Effectiveness\_2} \quad (1)$$

$$NB = Effectiveness \times WTP - Cost \quad (2)$$

At any given WTP threshold, the optimal treatment was the one with the highest NB. However, uncertainties around costs and effectiveness may reduce the confidence in the choice of optimal treatment. Therefore, value-of-information analysis was performed from PSA iterations and population EVPI (Expected value of perfect information) was plotted against a range of WTP threshold for the selection of an effective treatment.

RESULT AND DISCUSSION

Increase in antibacterial resistance against antibacterial drugs, especially beta-lactam drugs has put pressure on carbapenems use. The situation is becoming worse as excessive use of carbapenems is leading to emergence of resistance against this class of drug.[4] The focus of research community is to look for effective alternatives against bacterial pathogens in order to reduce the pressure on unchecked use of carbapenem. Recently, the fixed dose combination of beta-lactam (ceftriaxone) and beta-lactamase (sulbactam) have shown great potential against resistant pathogen, and advocate its candidacy as a carbapenem sparer drug. The effectiveness of the drug combination (or Elores®) has already been shown in literature.[8-11] However, in current scenario of limited resources, time and money, the economic evaluation of a new drug is important to predict its success in market. In the present study, we have performed an in-depth economic evaluation of Elores in comparison with meropenem to evaluate its potential as a carbapenem sparer drug.

Recent literature on Elores and meropenem was utilized for the present CEA,[12] where a clinical data of 65 patients were extracted to evaluate cost-effectiveness of the two treatment i.e. Elores and meropenem. The cost effectiveness analysis was done in two sections. First section was focused on evaluating cost-effectiveness of two approaches specifically used in the Bhatia et al.'s article.[12] In the study, colistin was additionally administered to cure the patients infected with meropenem or Elores resistant pathogens and thus becomes integral part of the approach and the CEA calculations.[12] In the second section, colistin component was excluded from the dataset, and the CEA of Elores and meropenem treatments were performed using probabilistic sensitivity analysis in order to make the analysis more informative and widely applicable.

Cost effective analysis of approaches used in Elores and meropenem treated groups

Demographics of all the patients were reported in literature.[12] Briefly, 65 patients were selected; out of which 31 were treated with meropenem (G-1) and the rest were treated with Elores (G-2) (Figure 1). Out of 31 patients of G-1, 19 patients were cured and the remaining ones were administered with the colistin + meropenem. Failures were still observed in five patients, which were then treated with Elores+ colistin to get complete cure. In Elores treated group (G-2), only 8 failure cases were observed, which were cured with colistin + Elores.

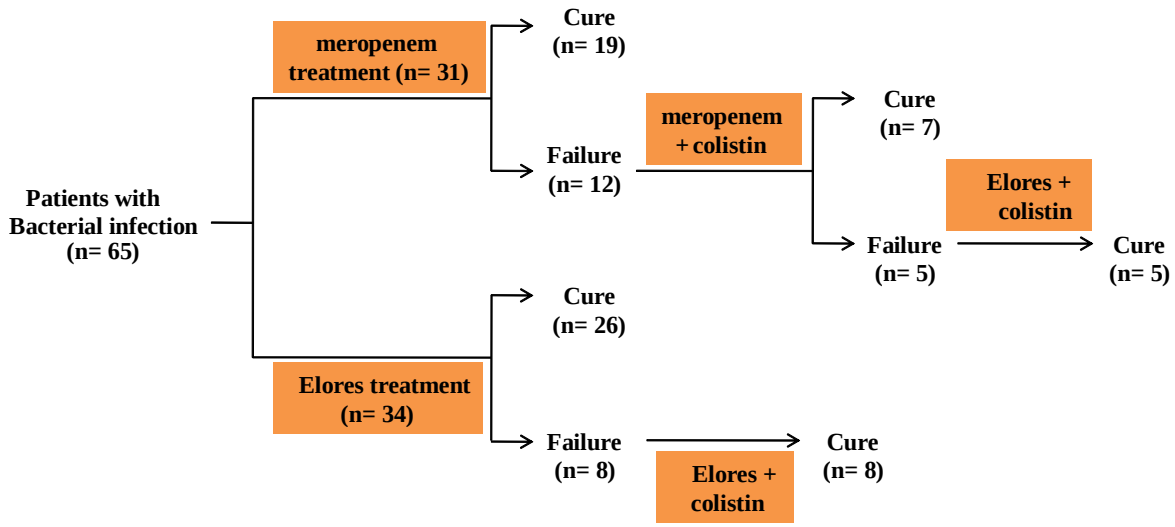


Figure 1: Schematics of meropenem and Elores treatment employed in the treatment of hospital acquired infections[12]

In cost-effectiveness analysis, cost and efficacy of two approaches i.e. Elores treated group and meropenem treated groups were calculated and compared. Focusing on cost of therapy, both direct and indirect costs were included to calculate total cost of therapy (Table 1). The total cost of therapy for meropenem treated groups was INR 1,38,051 (USD 2124), whereas the same for Elores was INR 1,09,307 (USD 1681.6). The higher cost associated with meropenem treated groups was due to primarily two reasons i.e. high dose frequency and longer duration of treatment.[13] In terms of dose frequency, thrice-a-day dosing was recommended for meropenem group, whereas twice-a-day dosing was prescribed to Elores treated groups which translates into higher antibacterial cost. Focusing on duration of therapy, higher failures were observed in meropenem group (38.7% vs. 23.5% of Elores group), which were then treated with colistin. Failures were still observed in the group, and Elores + colistin combination was then used to cure all patients, which thus increased the net duration of therapy adding to personnel and indirect cost. However, in Elores treated groups, fewer failure cases (23.5%) were observed and all of them were treated effectively with colistin treatment. Higher duration of treatment translates into higher overall cost of therapy for meropenem treated group. For instance, antibacterial cost of meropenem group of INR 54,764 (USD 842.5) was higher than that of Elores treated group. Also, personnel cost of meropenem treated group of INR 70,403 (USD 1,083) was higher as compared to that of Elores treated group i.e. INR 60,000 (USD923). The same observation was recorded for indirect cost of treatment. However, other costs associated with diagnostic test, renal function test, transport cost were in same range for both groups as it were applied to both therapy equally irrespective of duration of therapy and dose frequencies.

Table 1: Different cost components used to calculate cost of therapy per patients for meropenem and Elores treated groups against HAIs; II. Cost of therapy per patient for various perspectives was shown; III. Cost effectiveness ratio of Elores and meropenem for HAI treatment was also presented; 1 USD=65 INR

S.no.	Cost component	Cost of Antibacterial treatment options	
		meropenem treated group INR (US$)	**Elores treated group INR (US$)**
1	Antibacterial cost	54,764 (842.5)	37,888(582.9)
2a	Diagnostic test	2,860 (44)	2,860(44)
2b	Renal function test	137 (2.1)	59(1)
3	Personnel cost	70,403 (1,083)	60,000(923)
4	Transport cost	500 (7.7)	500(7.7)
5	Indirect cost	9,387 (144.4)	8,000(123)
II. Cost of therapy for various perspective			
1	Societal perspective (drug, diagnostic, personnel, transport, and indirect cost)	1,38,051 (2,124)	1,09,307 (1,682)
2	Health care perspective (drugs, diagnostic, personnel)	1,28,164 (1,972)	1,00,807 (1,551)
3	Third party payer perspective (drugs, diagnostic costs)	57,761 (889)	40,807 (628)
III. Cost Effectiveness ratio			

1	Cost of drug for 7 days	14,247 (219)	13,196 (203)
2	Cost of therapy (societal) for 7 days	99,729 (1,534)	92,372 (1,421)
3	Effectiveness	73.65	81.57
4	Cost effectiveness ratio	1,354.09	1,132.44

The cost of therapy can be analyzed using different perspectives i.e. societal, health care and third party payer prospective. In general, the cost of therapy of both treatment (Elores and meropenem) approaches was much lower for third party payer as compared to societal and health care perspectives due to the exclusion of personnel, transport and other direct costs in third party payer perspectives (Table 1). Since, the focus of the study was to evaluate the cost-effectiveness of Elores treatments for the patients, the cost of therapy was calculated from societal perspectives. On comparing cost of therapy of Elores [i.e. INR 1,09,307 (USD 1,682)] and meropenem [i.e. INR 1,38,051 (USD 2,124)], Elores was less expensive due to its shorter duration of therapy and dose frequency.

Health benefits associated with the strategies under comparison can be measured by using natural units of outcome (i.e. life-years), number of infections, or utilities. In the present study, we have measured the treatment efficacy in terms of 'effectiveness rating', which collectively includes degree of efficacy, adherence tendency and humanistic outcomes (Table 2). The degree of efficacy of both drug treatments were obtained from *in-vitro* susceptibility testing of 95 bacterial isolates.[12] Elores was higher (88.40%) in efficacy as compared to meropenem (78.14%) against bacterial isolates tested. In terms of adherence tendency, Elores outweighs meropenem because of its twice-a-day regimen as compared to thrice-a-day dosing of meropenem. The humanistic outcomes were almost similar in both approaches as both are well tolerated drugs with minimal adverse effects. The total 'effectiveness measures' of meropenem was 73.65 %, which was lower than that (81.57 %) of Elores. The effectiveness measures of both treatments were then correlated with their corresponding cost of therapy in order to compute the cost-effectiveness of both treatments (Table 1). Duration of therapy was taken as 7 days for computation as it is an average duration of therapy for most of the antibiotics available commercially. As shown in Table 1, cost-effectiveness of Elores treatment had a lower cost effective ratio (CER) of 1132.44, as compared to that of meropenem (i.e. 1354.09), showing its superiority against meropenem strategy. To summarize, Elores treated group was more cost-effective treatment (lower CER) as compared to meropenem treated group against the bacterial isolates of HAIs.

Table 2: Effectiveness component used to calculate effectiveness measures per patients for meropenem and Elores treated groups against hosptial acquired infections (HAIs).

S.no.	Effectiveness component	meropenem treatment			Elores treatment		
		Value (%)	Assigned weights	Criterion rating	Value (%)	Assigned weights	Criterion rating
1	Degree of Efficacy	78.14	0.5	39.07	88.40	0.5	44.2
2	Adherence tendency	34.87	0.2	6.97	47.24	0.2	9.45
3a	Humanistic outcomes (Local effect/tolerability)	91.33	0.1	9.13	92.53	0.1	9.25
3b	Humanistic outcomes (ADR rating/tolerability)	92.34	0.2	18.47	93.34	0.2	18.67
	Sum of criteria rating (Effectiveness measures)	NA	1	73.65	NA	1	81.57

Cost effective analysis of Elores and meropenem treated groups using probabilistic sensitivity analysis

Economic evaluation provides a framework to allocate resources to effective strategies, and guide in decision making with understanding the value for money of each strategy.[22, 23] It is measured in terms of incremental effectiveness ratio (ICER) which basically assesses the additional cost that one treatment would impose over another treatment in lieu of benefits it provides. The present study had evaluated the cost-effectiveness of Elores and meropenem using probabilistic sensitivity analysis (PSA) as it incorporates uncertainty in the model parameters and provide more confidence in decision making of resource allocations (Figure 2).[21] The input parameters and output of the PSA were summarized in Table 3. For the analysis, beta and normal distributions were assigned to transition probabilities (of both treatment) and cost of therapy (of meropenem) respectively; and Monte Carlo simulations (N=1000 iterations) were performed. For each iteration, the values from distributions were selected to give sample of values of all parameter of interest. These samples were then subsituted into the model and the model was recalculated for 1000 times to generate full set of expected values which reflected different combination of parameter values.

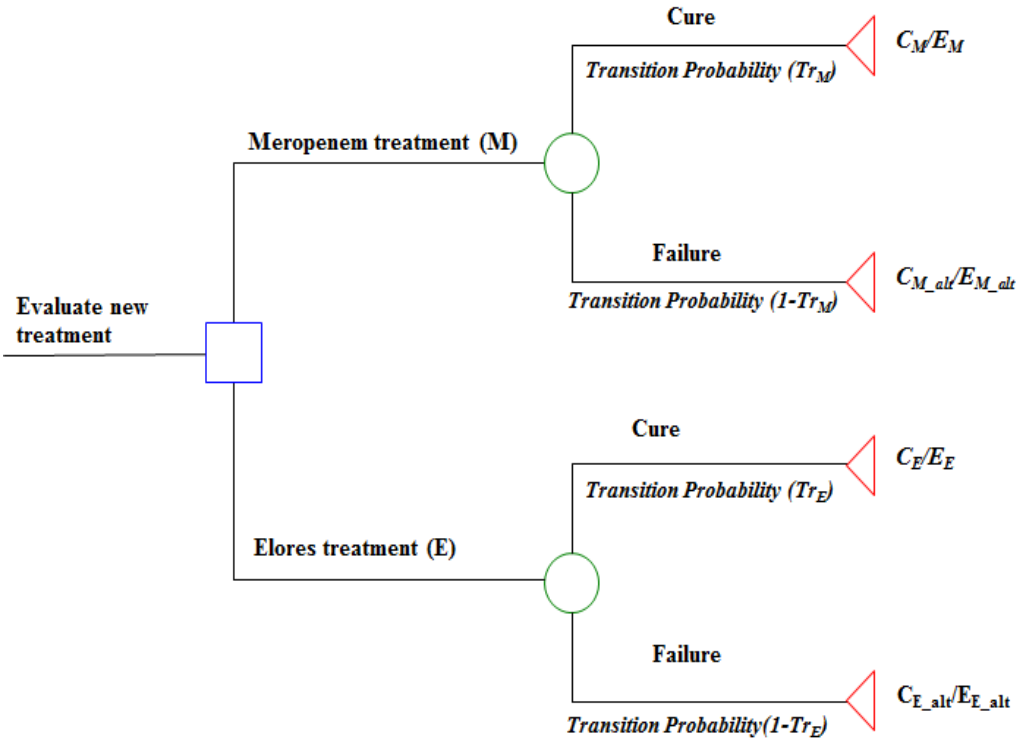


Figure 2: Decision tree was constructed to evaluate the cost-effectiveness of Elores treatment in comparison with meropenem against HAIs using probabilistic sensitivity analysis. M: meropenem; M_alt: no meropenem; E: Elores; E_alt: no Elores; Tr: transition probability; C: cost; E: effectiveness.

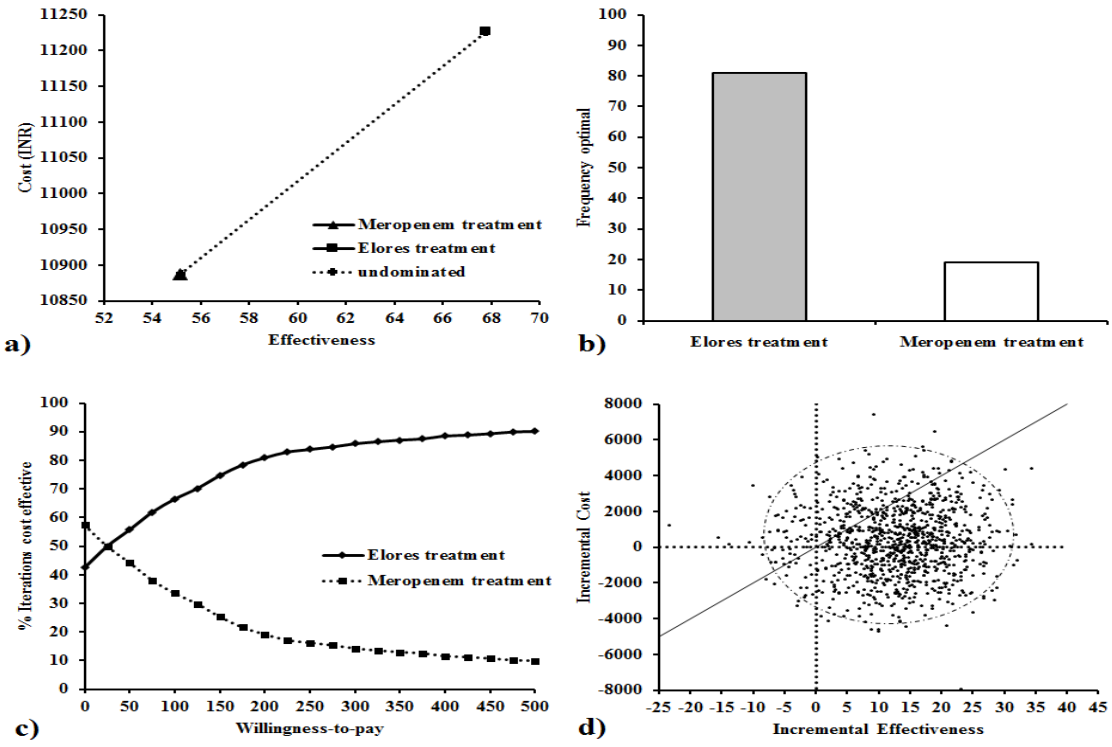
The results of PSA were summarized in Figure 3. Figure 3a has shown the CEA of the base-case in which the model used mean values from all of the iterations and constructed the 'undominated' line between Elores and meropenem strategies, which indicates the change in cost with the change in effectivensss. The estimated ICER from the line was INR 26.84 per unit of effectiveness (Table 3). None of the treatment dominated in the base-case analysis, which means Elores effectiveness over meropenem treatment comes with an additonal cost of INR 26.84. An optimal intervention is one with an ICER that is not more than the decision maker's intrinsic valuation for an additional unit of the outcome.[22, 23] The ICER for Elores treatment was quite low which already supported Elores treatment. However, the base case analysis does not incorporate the uncertainty in the model parameters and might lead to false interpretation of the results. To avoid the problem, decision makers' willingness-to-pay (WTP) was set to INR 200 per unit of effectiveness measures after considering the low ICER of base-case analysis and cost difference of both anti-bacterial drugs. Figure 3b has shown the net benefit strategy selection at WTP of INR 200, in which 80% of the Monte Carlo iterations (out of 1000 iterations) favored Elores treatment as compared to 20% iterations favoring meropenem. In other words, there is 80% of chance that Elores would be cost-effective at WTP of 200. To get more confidence in the results of base-case analysis, cost effective acceptality curves were generated to see what percentage of iterations favors Elores relative to meropenem treatment against varying values of WTP (Figure 3c). The WTP was ranged from INR 0 to 500 and iterations favoring both treatments were observed. Iterations favoring Elores treatments started from WTP ~27 (50% favorable iterations) and culminates around WTP ~250 (82% favorable iterations. The results clearly suggested that Elores treatment outweighed its effectiveness over meropenem with a minor increase in WTP, and thus would be a better cost-effectiveness option. Figure 3d have shown incremental cost effectiveness (ICE) scatterplot of all simulations and solid line was drawn at WTP~200. Each point in the ICE scatterplot represented a pair of values which showed incremental cost and effectiveness for that simulation. More than 80% points were below the WTP line, supporting the cost-effectiveness of Elores strategy over Meropenem at the given WTP. Also, there were quite a few points at/around the origin which mean that there was no change in cost and effectiveness with the change in treatment in many simulations, which supports Elores candidacy as a carbapenem sparer drug considering the uprising resistance against carbapenem class of drugs.

Table 3: Model input parameters, distributions, and ranges utilized in decision tree analysis to assess the cost effectiveness of meropenem and Elores using Probalisitic Sensitivity analysis (PSA) along with the results.

Model input parameters					
Treatment	**Cost of treatment INR (US $) [assigned distribution, std dev]**		**Effectiveness measures**	**Transition probability for cure [assigned distribution, std dev]**	
meropenem	11,226 (173) [fixed value]		83.9	0.61 [beta, 0.2]	
Elores	10,955 (169) [normal,2000]		73.36	0.76 beta,0.2]	
Model output parameters					
Treatment	**Cost INR (US $) [95% CI]**	**Effectiveness [95% CI]**	**Incremental Cost INR(US$)**	**Incremental Effectiveness**	**ICER**
meropenem	10,888 (168) [6,951-14,517]	55.2 [45.4-63.4]	--	--	--
Elores	11,226 (173)	67.8 [53-79]	338 (5.2)	12.61	26.84

Another approach i.e. net benefit framework was employed in the PSA to make it more informative and useful. Net monetary benefit (NMB) basically transforms cost and effectiveness into monotonic linear function (Equation 2). As shown in Figure 3e, higher effectiveness of Elores treatment provides higher slope value to Elores NMB linear function and thus results in upward line as compared to meropenem NMB line. Similar intercept (~ -11,000 INR) for both Elores and meropenem treatment undermines the effect of cost and strengthen the importance of effectiveness in cost-effective analysis of the two drug treatments.

In decisions making, the allocation of healthcare resource are not only based on estimated cost-effectiveness (CE) of different strategies, but also on the value of additional research designed to reduce uncertainty in the decision.[24, 25] Expected-value-of-perfect-information (EVPI) is the amount that a decision maker should be willing to pay to reduce uncertainties regarding the decision of optimal treatment. Further research is potentially cost-effective only when the EVPI is more than the expected research costs. In the present case, EVPI value was quite low i.e. 290 (especially at the WTP of INR 200) as compared to estimated cost of research, which eliminated the needs for additional research for decision making (Figure 3f). The peak in the curve were observed at a WTP threshold of INR 26 corresponding to an EVPI of INR ~780, which means that the expected benefit of further research to reduce decision uncertainty would be highest at this WTP threshold (Figure 3f). This values corresponds to the region between WTP thresholds of INR 25-50 in the CE acceptability curve of the base-case analysis (Fig. 3c), where there was considerable uncertainty regarding the choice between Elores and meropenem for optimal treatment.



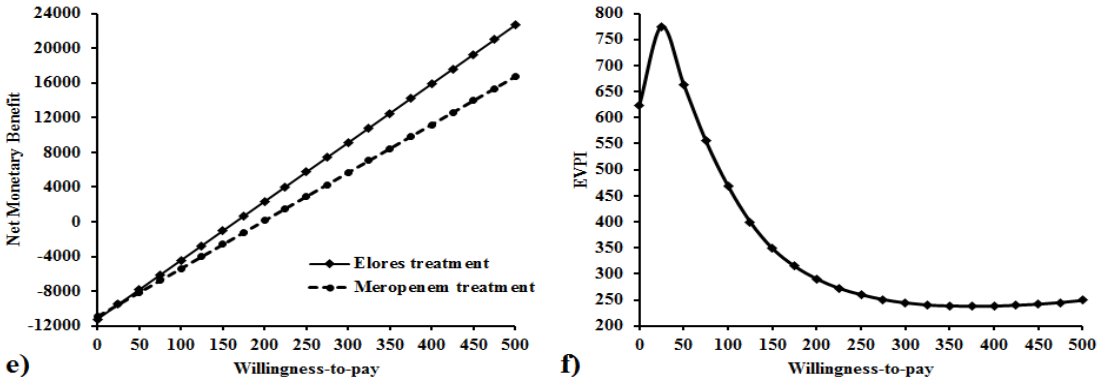


Figure 3: (a) Cost effective analysis (CEA) of Elores and meropenem treatment in base-case analysis; (b) CEA analysis of both treatments at willingness-to-pay (WTP) threshold of INR 200 per unit of effectiveness measures; (c) Cost effectiveness acceptability curve of both treatment strategies against HAIs showing the proportion of model iterations favouring the treatments at a given WTP threshold; (d) Incremental cost effectiveness scatterplot showing results of all iterations plotted between incremental cost and incremental effectiveness. Solid line represents WTP of INR 200 and elipssis showed 95 % CI; (e) Net monetary benefits (NMB) vs WTP curve have shown upward line for Elores which underlines the superiority of Elores effectiveness in CEA analysis as compared to meropenem treatment; (f) Expected-value-of-perfect-information (EVPI) at a given WTP threshold provides the information on the need of additional research to reduce the uncertainty in optimal decision making

The main strength of the study was the use of relatively new efficacy data for both treatments from the study locality as the literature reported efficacy value often drops over time partly because of the development of acquired resistance. Other strengths were the inclusion of various cost components including indirect cost and the comparison with other perspectives which can increase the applicability of the results. The robustness of the analysis was strengthened by probabilistic sensitivity analysis which accounts for the uncertainty in model parameters and help in making optimal decision.

Major limitations of the first section of the study were small clinical dataset, accuracy in cost of treatment, the reliance on susceptibility data as a proxy cure rate, and the difficult accuracy in the allocation of assigned weights to the various outcomes.[26] In real setting, a consensus between the researcher and policy makers would minimise these drawbacks. It must be mentioned that both strategies were treated in the same way, which thus limited the subjectivity of the study. For addressing the above-mentioned shortcomings, probabilistic sensitivity analysis was carried out to account for uncertainty in model parameters;[27] and their impact on the CEA of Elores and meropenem treatment was successfully evaluated.

CONCLUSION

The present study have presented the first cost-effectiveness analysis of fixed dose combination of ceftriaxone and sulbactam (i.e. Elores®) in comparison with meropenem treatment. The PSA results have shown that the Elores treatment is a cost-effective use of resources as compared to carbapenem drugs, and thus supports its candidacy as a carbapenem sparer drug to prevent further morbidity and mortality.

ACKNOWLEDGEMENT

Authors acknowledges Venus Medicine Research Center for financial support. Authors are also grateful to the reviewers of this materials for their valuable suggestions and corrections.

Conflict of Interest

There is no conflict of interest associated with this study.

REFERENCES

1. Geneva, World Health Organization. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioural factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Inf Dis, 1999; 5: 1.
2. Sitthi-amorn C, Ratana Somorongthong R, Janjaroen WS. Economic and Health care restructuring-the need for better governance. Int J of Epidemiol, 2001; 30: 717-719.
3. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, Lynfield R, Maloney M, McAllister-Hollod L, Nadle J, Ray SM, Thompson DL, Wilson LE, Fridkin SK. Multistate point-prevalence survey of health care-associated infections. *N* Engl J Med, 2014; 370: 1198-208.
4. Cornaglia G, Rossolini GM. The emerging threat of acquired carbapenemases in Gram-negative bacteria. Clin Microbiol Infect, 2010; 16: 99-101.
5. Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hedge A, Soman R. New Delhi Metallo-beta lactamase (NDM-1) in Enterobacteriaceae: treatment options with carbapenems compromised. J Assoc Physicians India, 2010; 58: 147-9.
6. Mehta KC, Dargad RR, Borade DM, Swami OC. Burden of Antibiotic Resistance in Common Infectious Diseases: Role of Antibiotic Combination

Therapy. J Clin Diagn Res, 2014; 8(6): ME05–ME08.

7. Chaudhary M and Payasi **A.** A randomized, open label prospective, multicenter phase-III clinical trial of Elores in lower respiratory tract and urinary tract infections**.** *J Pharmacy Res.* 2013; **6**:409-414.
8. Chaudhary M, Payasi A. Clinical, microbial efficacy and tolerability of Elores, a novel antibiotic adjuvant entity in ESBL producing pathogens: Prospective randomized controlled clinical trial. J Pharmacy Res. 2013; 6: 275-280.
9. Sharma VD, Singla A, Chaudhary M, Taneja M. Dose optimization of ceftriaxone-sulbactam combination in adults using *in-vitro* systems, PK/PD modeling and stochastic simulations approaches. Int J Pharm Pharm Sci, 2016; 8(7):00000. http://www.innovareacademics.in/journals/index.php/ijpps/article/view/12137
10. Sharma VD, Singla A, Chaudhary M, Taneja M. Dose optimization of ceftriaxone-sulbactam combination in pediatric using in-vitro systems and stochastic simulation approaches. Int J Pharm Sci Res, 2016; 7(4): 1503-12.
11. Sharma VD, Singla A, Chaudhary M, Taneja M. Population pharmacokinetics of fixed dose combination of ceftriaxone and sulbactam in healthy and infected subjects. AAPS PharmSciTech 2015; doi: 10.1208/s12249-015-0454-2.
12. Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: a new way to spare carbapenems. Res J Infect Dis 2015; 3(2). http://dx.doi.org/10.7243/2052-5958-3-2.
13. Product monograph: meropenem. http://www.drugs.com/monograph/meropenem.html
14. Hodgson TA, Meiners MR. Cost of Illness Methodology: A guide to current practices and procedures. Milbank Memorial Fund Quart, 1982; 60(3): 429-462.
15. Suleiman IA, Bamiro BS and Tayo F. Cost Effectiveness of three drug for the treatment of S aurues in Nigeria. Int J of Clin Pharm, 2012; 34: 739-745. DOI 10.1007/s11096-012-9671-x
16. Suleiman IA, Tayo F. Pharmacoeconomic evaluation of antimicrobial agents in the treatment of sexually transmitted diseases in Lagos University Teaching Hospital. West African J Pharmacy, 2004; 18 (1): 42-52.
17. Cano SB, Fujita NK. Formulary evaluation of third generation cephalosporins using decision analysis. Am J of Hosp Pharm, 1988; 45-566-9
18. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making, 1993; 13(4): 322–338
19. Hunink M, Glaziou P, Siegel J, Weeks J, Pliskin J, Elstein A. Decision Making in Health and Medicine. Integrating Evidence and Values. Cambridge, UK: Cambridge University Press., 2001.
20. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making, 1985; 5(2): 157–177.
21. Briggs A, Sculpher M, Klaxton C. Decision Modelling for Health Economic Evaluation. New York, NY: Oxford University Press., 2006.
22. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford, UK: Oxford University Press., 2005.
23. Gold MR, Siegel JE, Russel LB, Weinstein MC. Cost Effectiveness in Health and Medicine. New York, NY: Oxford University Press., 1996.
24. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research: some lessons from recent UK experience. Pharmacoeconomics, 2006; 24(11): 1055-1068.
25. Barton GR, Briggs A, Fenwick EA. Optimal Cost-effectiveness: The role of Cost-effectiveness Acceptability Curve (CEAC), the Cost-Effectiveness Acceptability Frontier (CEAF), and the Expected Value of Perfection Information (EVPI). Value in Health, 2008; 11: 886-97
26. Suleiman IA, Bamiro BS, Mendie U. Cost effectiveness of six drugs for the treatment of *Psuedomonas aeruginosa* infections in Nigeria. Int J Pharm Pharm Sci, 2014; 6(5): 239-244.
27. Ting J, Tien Ho P, Xiang P, Sugay A, Abdel-Sattar M, Wilson L. Cost-Effectiveness and Value of Information of Erlotinib, Afatinib, and Cisplatin-Pemetrexed for First-Line Treatment of Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer in the United States. Value in Health, 2015; 18(6): 774-82.