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Cost-Effectiveness of Meropenem Versus Ceftriaxone for the Treatment of Sepsis at Dr. Tadjuddin Chalid Hospital Makassar

Anshar Saud[1*], Alfira Mutmainnah[1], Bustanul Arifin[1,2]

Artikel Penelitian

Abstract: *Sepsis is a critical condition arising from the body's response to an infection. In Indonesia, the incidence of sepsis remains notably high, with mortality rates reaching 49%. At Dr. Tadjuddin Chalid Hospital Makassar, meropenem and ceftriaxone are extensively utilized as empirical therapies. Conducting a cost-effectiveness analysis is essential for ensuring rational and efficient decision-making in the selection of appropriate antibiotic therapy. This study aimed to compare the cost-effectiveness of meropenem versus ceftriaxone in treating patients with sepsis in the inpatient ward of Dr. Tadjuddin Chalid Hospital Makassar. A retrospective cross-sectional design was employed, utilizing the medical records of patients with sepsis. Data were analyzed using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER) to ascertain the economic value of both antibiotics. The results indicated that the ACER value of meropenem was IDR 731,180.68, which was lower than that of ceftriaxone (IDR 775,021.41), suggesting that meropenem was more cost-effective. The incremental cost of IDR 667,206 indicates the additional expenditure required for meropenem to achieve a 1% increase in the proportion of patients with a length of stay of less than 17.4 days. The sensitivity analysis results align with the ICER analysis, which identified meropenem as more cost-effective, enabling robust conclusions. Treatment costs emerge as the key variable affecting the ICER, requiring primary consideration when interpreting cost-effectiveness results. In conclusion, meropenem is more cost-effective than ceftriaxone and can be recommended as an alternative antibiotic therapy for patients with sepsis from a pharmacoeconomic perspective.*

Keywords: *Meropenem, Cost-effectiveness Analysis, Ceftriaxone, Makassar*

Abstrak: Sepsis adalah kondisi kritis yang timbul akibat respons tubuh terhadap infeksi. Di Indonesia, angka kejadian sepsis masih sangat tinggi, dengan angka kematian mencapai 49%. Di Rumah Sakit Dr. Tadjuddin Chalid Makassar, meropenem dan seftriakson banyak digunakan sebagai terapi empiris. Melakukan analisis efektivitas biaya sangat penting untuk memastikan pengambilan keputusan yang rasional dan efisien dalam pemilihan terapi antibiotik yang tepat. Studi ini bertujuan untuk membandingkan efektivitas biaya meropenem versus seftriakson dalam pengobatan pasien sepsis di ruang rawat inap Rumah Sakit Dr. Tadjuddin Chalid Makassar. Desain retrospektif potong lintang digunakan, dengan memanfaatkan rekam medis pasien sepsis. Data dianalisis menggunakan Average Cost-Effectiveness Ratio (ACER) dan Incremental Cost-Effectiveness Ratio (ICER) untuk memastikan nilai ekonomi kedua antibiotik tersebut. Hasil penelitian menunjukkan bahwa nilai ACER meropenem adalah Rp 731.180,68, yang lebih rendah daripada seftriakson (Rp 775.021,41), menunjukkan bahwa meropenem lebih hemat biaya. Rasio efektivitas biaya inkremental sebesar Rp 667.206 menunjukkan pengeluaran tambahan yang dibutuhkan untuk meropenem guna mencapai peningkatan 1% pada proporsi pasien dengan lama rawat inap kurang dari 17,4 hari. Hasil analisis sensitivitas selaras dengan analisis ICER, yang mengidentifikasi meropenem sebagai obat yang lebih hemat biaya, sehingga memungkinkan kesimpulan yang kuat. Biaya pengobatan muncul sebagai variabel kunci yang memengaruhi ICER, sehingga perlu dipertimbangkan secara utama saat menafsirkan hasil efektivitas biaya. Kesimpulannya, meropenem lebih hemat biaya daripada seftriakson dan dapat direkomendasikan sebagai terapi antibiotik alternatif untuk pasien sepsis dari perspektif farmakoekonomi.

Kata kunci: Meropenem, Analisis Efektivitas Biaya, Seftriakson, Makassar

[1] Department of Pharmacy, Faculty of Pharmacy, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[2] Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen,

Korespondensi:

Anshar Saud
ansharsaud@unhas.ac.id

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Introduction

Sepsis is a serious condition caused by the body's response to infection that can progress to organ dysfunction and even death. Etymologically, the term sepsis comes from the Greek word "sepo," meaning decay, and is medically defined as a systemic infection that causes a widespread inflammatory response in the body. The organisms most commonly responsible for sepsis include Gram-positive bacteria, such as *Staphylococcus aureus*, and Gram-negative bacteria, such as *Pseudomonas* and *Escherichia coli* (1,2).

The 2019 Global Burden of Disease (GBD) Antimicrobial Resistance Collaborators reported more than 6 million deaths worldwide due to bacterial infection syndromes, including lower respiratory tract infections, bloodstream infections, and peritoneal or intra-abdominal infections. In Indonesia, the prevalence of sepsis was reported to reach 30.29%, with a mortality rate of 11.56–49%. Effective treatment of sepsis includes administering broad-spectrum antibiotics within the first hour of diagnosis to improve patient survival (3–5).

According to the National Guidelines for Medical Services for Sepsis Management-Indonesian Ministry of Health (2017), antibiotic therapy should be initiated immediately after confirming a sepsis diagnosis. This follows a de-escalation strategy, where empirical antibiotics are administered and adjusted based on clinical response or culture results. Empirical antibiotic therapy using broad-spectrum antibiotics may be given as monotherapy or in combination, targeting potential causative bacteria based on clinical syndromes and bacterial patterns (antibiograms). Suitable broad-spectrum antibiotics include carbapenems, fourth-generation cephalosporins, piperacillin, and tazobactam (6).

Ceftriaxone and carbapenems are viable pharmacological options for inclusion in both community-acquired and hospital-acquired antimicrobial treatment regimens. These drugs are recommended for use either as monotherapy or in conjunction with other agents, contingent upon the anatomical site of the sepsis infection, which may include the urinary tract, respiratory system, intra-abdominal region, or cases where the infection site is indeterminate (7).

At Dr. Tadjuddin Chalid Makassar, Indonesia, the antibiotics utilized for empirical therapy include meropenem and ceftriaxone. Meropenem, classified as a carbapenem antibiotic, functions by inhibiting bacterial cell wall synthesis, while ceftriaxone, a third-generation cephalosporin, operates through a similar mechanism. The selection of antibiotics is guided not only by clinical efficacy but also by cost-effectiveness, given that the treatment of sepsis patients requires substantial medical resources (7,8).

Current literature reveals an absence of studies that directly compare the cost-effectiveness of meropenem and ceftriaxone in the treatment of sepsis, whether on an international, national, or local scale. Nonetheless, some data regarding the cost and efficacy of these two antibiotics are available. Ceftriaxone is frequently selected as the first-line treatment for sepsis in several developing countries due to its availability at no cost, whereas meropenem is employed as a second-line treatment owing to its higher expense and associated out-of-pocket costs (9).

Research conducted at Siloam Hospital Manado in 2019 revealed that meropenem was more cost-effective than ceftazidime and cefotaxime. In contrast, a study by Ruflianasari et al. (2024) found that ceftriaxone was more cost-effective than meropenem for the treatment of hospital-acquired pneumonia (10,11).

This study serves as a preliminary local investigation to assess the cost-effectiveness of meropenem and ceftriaxone in treating sepsis. The research evaluates costs associated with sepsis patient care, including pharmaceutical and healthcare service expenses. It seeks to compare the cost-effectiveness of meropenem and ceftriaxone using Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER) parameters. The findings of this study are expected to improve rational and cost-effective decision-making concerning antibiotic therapy for sepsis at Dr. Tadjuddin Chalid Makassar. Additionally, they are anticipated to provide a foundation for future research on pharmacoeconomic policy related to sepsis patients in Indonesia.

Materials and Methods

Materials

The materials used were the medical records of inpatients at Dr. Tadjuddin Chalid Hospital, Makassar, in 2023. The collected data included patient identity, sepsis diagnosis, source of infection, physical examination results, length of stay, and antibiotic therapy data, including intravenous meropenem or ceftriaxone for at least three days.

Methods

The research employed a descriptive observational cross-sectional design, utilizing a retrospective approach through the examination of patient medical records. The study population comprised all patients diagnosed with sepsis who were hospitalized during the study period. The sample was selected using purposive sampling based on the following inclusion criteria: patients with sepsis who received either meropenem or ceftriaxone therapy for a minimum of three days and had complete medical records. Patients were excluded if they were discharged involuntarily, had immunocompromised conditions (such as HIV/AIDS or advanced cancer), died during therapy, or altered their antibiotic regimen.

Data Analysis

1. Percentage of patients receiving meropenem or ceftriaxone antibiotic therapy.
2. Average length of stay. Length of stay was calculated using the AvLOS formula (12):

   AvLOS = Total number of inpatient days ÷ Total number of discharged patients
3. Percentage of drug effectiveness in hospitalized patients with sepsis using the total significant efficacy formula (13):

   % Effectiveness = (Number of patients with effective outcome ÷ Total number of patients in the group) × 100%

This effectiveness value was used as the basis for calculating the ACER and ICER to compare the cost efficiency of each antibiotic therapy.

The Patient Care Process for Sepsis necessitates the monitoring of parameters, including efficacy indicators such as signs and symptoms of infection, mental status, mean arterial pressure (MAP), lactate levels, and white blood cell (WBC) count with differential, as well as drug safety (7). Clinical outcomes that can be specifically measured and used as parameters of effectiveness: MAP <65 mmHg; Lactate <18 mg/dL (2 mmol/L); and WBC count with differential of 4.4–11 × 10^3 cells/µL (7,14). However, clinical outcome data, including MAP, lactate, and WBC with differential, are not consistently available in hospital settings, thereby necessitating the consideration of alternative parameters, such as length of stay.

Several researchers have proposed that a cost-effectiveness analysis between two pharmaceutical agents can be conducted by assessing the length of hospital stay (LOS) for patients treated with each drug. LOS is also a major driver of healthcare costs, making it a relevant and practical outcome measure for economic evaluations of pharmaceutical agents (15-17).

Consequently, the primary outcome parameter assessed in this study was the attainment of a hospital stay duration of less than 17.4 days, in alignment with the standards set by the Ministry of Health of the Republic of Indonesia (18).

4. Calculation of ACER and ICER (19):

   ACER = Total Cost of Treatment ÷ Effectiveness

ACER is the total cost of a program or treatment alternative divided by the clinical outcome to produce a ratio representing the cost per unit of each clinical outcome achieved.

ICER = (Cost of Treatment B - Cost of Treatment A) ÷ (Effectiveness of Treatment B - Effectiveness of Treatment A)

Comparing the ACER between treatment alternatives indicates the additional costs required to achieve increased effectiveness. The ICER formula can determine the additional costs when switching from drug A to drug B; the lower the additional costs, the more feasible the drug is (20).

The use of ICER in cost-effectiveness analysis is limited by interpretational ambiguities, sensitivity to small changes in outcomes, and challenges in handling uncertainty. These limitations necessitate careful sensitivity analyses and, in some cases, consideration of alternative summary measures to support robust health economic decision-making (21-23).

5. Average total direct medical costs incurred (medical procedures, treatment, laboratory examinations, and antibiotics).
6. Sensitivity analysis assesses the robustness of cost-effectiveness analysis results by varying key model variables and assumptions. By modifying parameters such as costs, health effects, or discount rates, it determines whether the analysis conclusions remain consistent or change significantly (24).

Results and Discussion

Characteristics of Sepsis Patients

This study involved 63 hospitalized patients with sepsis who met the inclusion criteria. Based on patient characteristics, the majority were male (35 patients) (55.5%), and 28 were female (44.4%). These results align with those of Kereh et al. (2020) for Prof. Dr. R. D. Kandou Hospital in Manado and the study by Mulatu et al. (2021) in Ethiopia, which also showed that sepsis patients were more prevalent among males. However, sex was not the primary determinant of sepsis, but rather was influenced by immunological conditions, nutritional status, and environmental factors (3,4,25).

The age distribution of patients indicated that individuals aged ≥46 years constituted the largest group at 39.6%, followed by those aged ≤10 years at 34.9%. The characteristics of sepsis inpatients are detailed in Table 1. This observation is consistent with the findings of Tambajong et al. (2016), who reported that the incidence of sepsis increases with age, particularly among the elderly, due to a decline in immune system function (4).

Numerous studies have demonstrated that comorbidities can significantly impact the length of stay (LOS) and healthcare costs for patients with sepsis. In a multicenter study, factors such as organ transplantation (liver, heart, lung), multiple trauma, chronic diseases, and other comorbid conditions were found to be significantly associated with prolonged LOS and increased hospital costs in sepsis patients (26).

Another study similarly reported that sepsis patients with comorbidities such as hypertension and diabetes experienced a longer average LOS in both the ICU and hospital compared to patients without these comorbidities. Specifically, sepsis patients with diabetes exhibited the longest average ICU LOS (15 days), whereas those with liver cirrhosis had the shortest LOS (11 days). Furthermore, patients with diabetes or hypertension also had the longest average hospital LOS (30 days), while those with liver cirrhosis had the shortest LOS (27).

Some scholars contend that the inclusion of comorbidities in LOS-based sepsis cost-effectiveness analyses is problematic. This contention arises from the fact that LOS is significantly affected by external, non-clinical factors, the variable impact of comorbidities on LOS, the scarcity of comprehensive comorbidity data, and the notion that LOS often reflects institutional characteristics rather than the individual disease burden. Consequently, employing LOS as the primary endpoint in sepsis cost analyses necessitates a cautious approach, with careful consideration of these limitations (28-31).

Table 1. Characteristics of Sepsis Inpatients

Patient Characteristic	Category	Number of Patients	Percentage (%)
Gender	Male	35	55.6
	Female	28	44.4
Age	≤ 10 years	22	34.9
	11–28 years	6	9.5
	29–45 years	10	15.9
	≥ 46 years	25	39.7
Antibiotic Therapy	Meropenem	30	47.6
	Ceftriaxone	33	52.4
Length of Stay	< 17.4 days	38	60.3
	≥ 17.4 days	25	39.7

Antibiotic Effectiveness in Inpatients with Sepsis

The average length of stay (AvLOS) for the patients in this study was 17.4 days. This duration surpasses the optimal AvLOS standard of 6–9 days as established by the Indonesian Ministry of Health (2005) (18). Among the total patients, 38 (60.3%) had a length of stay of less than 17.4 days, while 25 (39.6%) had a length of stay of 17.4 days or more. Table 2 shows the effectiveness of antibiotics in sepsis inpatients. An AvLOS exceeding the standard indicates that inpatient care is longer than expected. The contributing factors include the patient's severe clinical condition, delayed diagnosis, complications during treatment, limited medical resources, and suboptimal care management. In cases of sepsis, intensive care, stabilization, continued antibiotic therapy, and ongoing monitoring contribute to prolonged hospital stays (32).

In the analysis of antibiotic efficacy, meropenem exhibited superior effectiveness compared to ceftriaxone, with efficacy rates of 76.66% and 45.45%, respectively. The determination of therapeutic effectiveness was based on the average length of stay (AvLOS), categorizing patients with a stay of less than 17.4 days as experiencing effective treatment, while those with a stay of 17.4 days or more were deemed to have ineffective treatment. These findings indicate that meropenem is associated with reduced hospital stays, thereby offering greater clinical efficacy than ceftriaxone.

Table 2. Effectiveness of Antibiotics in Sepsis Inpatients

Antibiotic Therapy	Effectiveness	Number of Patients	Percentage (%)
Meropenem	Effective	23	76.6
	Not Effective	7	23.3
Ceftriaxone	Effective	15	45.5
	Not Effective	18	54.5

Cost-effectiveness analysis of antibiotic therapy based on ACER

In terms of costs, the average total cost for patients receiving meropenem therapy was IDR 56,052,311, while for ceftriaxone it was IDR 35,224,722. The ACER analysis showed an IDR of 731,180.68 for meropenem and 775,021.41 for ceftriaxone. Therefore, although the cost of meropenem therapy is higher, its effectiveness is also better, resulting in a lower ACER value, indicating that meropenem is more cost-effective. Cost-Effectiveness Analysis of antibiotic therapy based on ACER is shown in Table 3.

Table 3. Cost-Effectiveness Analysis of Antibiotic Therapy Based on ACER

Antibiotic Therapy	Average Total Cost per Patient (IDR)	Effectiveness (%)	ACER (IDR /% Effectiveness)
Meropenem	56,052,311	76.66	731,180.68
Ceftriaxone	35,224,722	45.45	775,021.41

Cost-effectiveness analysis of antibiotic therapy based on ICER

Based on the cost-effectiveness analysis, meropenem demonstrated greater effectiveness than ceftriaxone but at a higher cost. This places meropenem in quadrant I (high effectiveness and high cost), whereas ceftriaxone is in quadrant III (low effectiveness and low cost). Table 4 shows the Cost-Effectiveness Analysis of antibiotic therapy based on ICER calculation. Therefore, an ICER analysis is required to assess the balance between additional costs and increased effectiveness (19).

The analysis results showed that meropenem therapy was 76.66% effective, which was higher than ceftriaxone's 45.45%. However, the average total cost per patient in the meropenem group was higher (IDR 56,052,311) than in the ceftriaxone group (IDR 35,224,722), with a cost difference of IDR 20,827,589. The difference in effectiveness between the two was 31.21%, resulting in an ICER of IDR 667,206 (Table 4). This value indicates that every one percent increase in effectiveness of meropenem therapy requires an additional cost of IDR 667,206, making it a relatively cost-effective therapy (20).

Sensitivity analysis

Sensitivity test results indicated that several cost variables influenced changes in the ICER value for sepsis therapy. The three main parameters tested were pharmaceutical, accommodation, and procedure costs. The range of variation in the ICER is indicated by the difference between the upper and lower limits for each parameter (±25%) (33). Procedure or treatment costs showed the largest range of change, at IDR 35,118,264, followed by ceftriaxone accommodation costs (IDR 12,241,209) and ceftriaxone costs (IDR 8,436,324). Sensitivity analysis results are shown in Table 5 below. Thus, treatment costs are a key factor influencing the cost efficiency of therapies. Conversely, the Tornado diagram showed pharmaceutical costs have a smaller impact on the ICER, as their variation is relatively smaller than that of the other two parameters (Figure 1). Therefore, it can be concluded that in the context of sepsis therapy, the primary focus in cost management should be on clinical treatment efficiency (34,35).

Table 4. Cost-Effectiveness Analysis of Antibiotic Therapy Based on ICER

Antibiotic Therapy	Average Total Cost per Patient (IDR)	Effectiveness (%)	ΔC (IDR)	ΔE	ICER (ΔC/ΔE)
Ceftriaxone	35,224,722	45.45	20,827,589	31.21	667,206
Meropenem	56,052,311	76.66			

Table 5. Sensitivity Analysis Outcomes of Meropenem versus Ceftriaxone in Sepsis Inpatients

Parameter	Lower Limit (IDR)	Actual (IDR)	Upper Limit (IDR)	Difference 1 (IDR)	Difference 2 (IDR)
Meropenem Cost	4,974,185	6,632,247	8,290,308	1,658,061	1,658,061
Ceftriaxone Cost	6,327,243	8,436,324	10,545,405	2,109,081	2,109,081
Meropenem Accommodation	5,306,508	7,075,345	8,844,181	1,768,836	1,768,836
Ceftriaxone Accommodation	9,180,906	12,241,209	15,301,511	3,060,302	3,060,302
Procedure Cost	26,338,698	35,118,264	43,897,830	8,779,566	8,779,566
Other Cost	1,312,500	1,750,000	2,187,500	437,500	437,500

The findings of this study suggest that meropenem demonstrates greater cost-effectiveness compared to ceftriaxone in the treatment of patients with sepsis. Nonetheless, these findings are constrained by the specific context of Dr. Tadjuddin Chalid Makassar and a relatively small sample size. Consequently, further research with a broader scope is necessary to enable generalization.

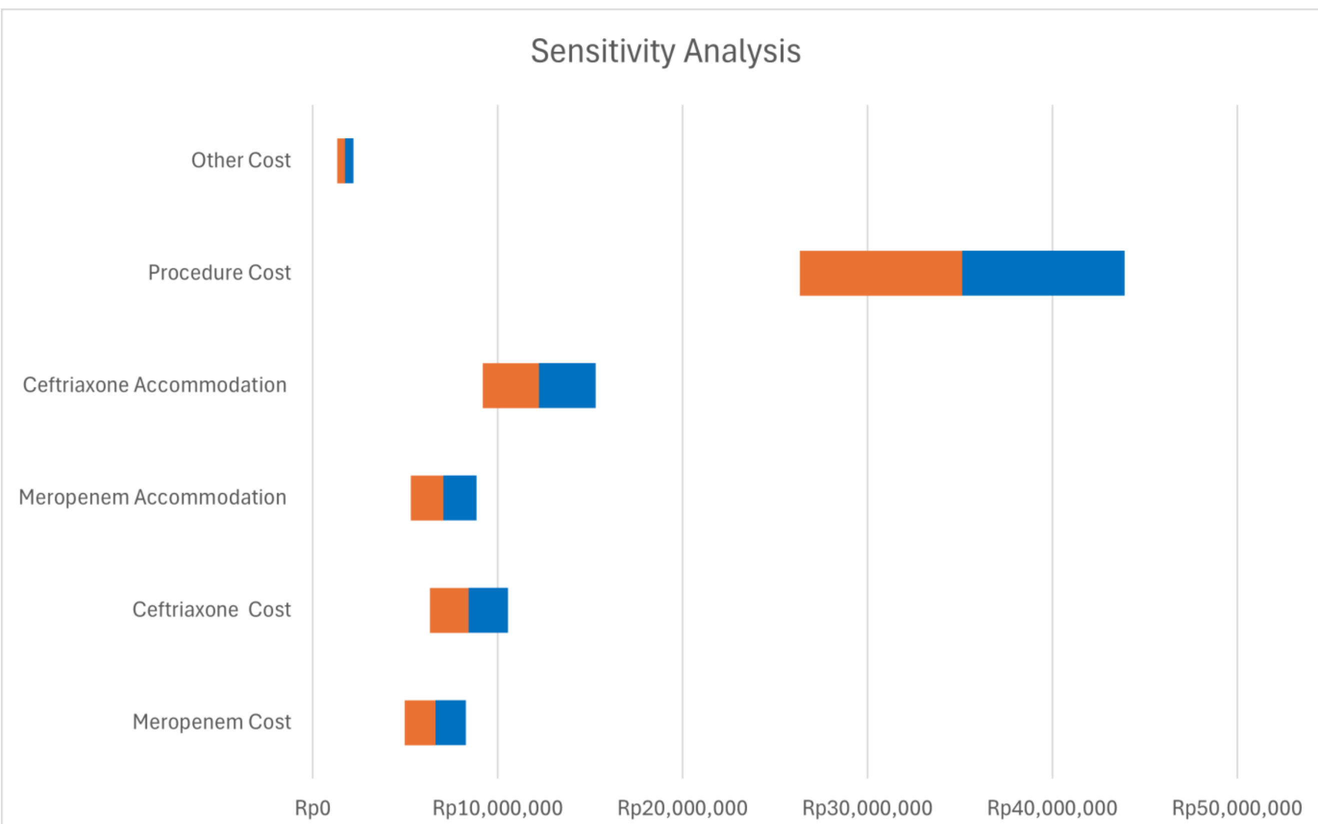

Figure 1. Sensitivity analysis tornado diagram comparing meropenem and ceftriaxone in sepsis inpatients. Parameters were varied by ±25% from the base-case values. Orange bars represent the lower limit values and blue bars represent the upper limit values for each parameter.

Conclusion

In the treatment of sepsis, meropenem therapy incurred a higher average total cost (IDR 56,052,311) compared to ceftriaxone (IDR 35,224,722). However, it resulted in a greater proportion of patients experiencing a length of stay of less than 17.4 days (76.66% versus 45.45%). The average cost-effectiveness ratio (ACER) for meropenem was IDR 731,180.68, which is lower than that of ceftriaxone at IDR 775,021.41. The incremental cost-effectiveness ratio (ICER) of IDR 667,206 indicates the additional expenditure required for meropenem to achieve a 1% increase in the proportion of patients with a length of stay under 17.4 days. The outcomes of the sensitivity analysis corroborate the findings of the ICER analysis, which identified meropenem as the more cost-effective option, thereby facilitating robust conclusions. Treatment costs emerge as the most significant variable influencing the ICER, necessitating primary consideration when interpreting the results of the cost-effectiveness analysis. From a pharmacoeconomic standpoint, meropenem can be considered a more cost-effective option compared to ceftriaxone for patients with sepsis.

Limitations

The primary outcome parameter evaluated was the length of stay, which is influenced by multiple factors and reflects the patient's clinical condition. Employing more specific clinical outcomes, such as monitoring mean arterial pressure (MAP), lactate levels, and white blood cell (WBC) counts with differential, may yield more precise results in cost-effectiveness analysis (CEA).

Patients who succumbed to their conditions were excluded from this study. However, in the analysis of clinical outcomes, sepsis patients who died during hospitalization were explicitly included in the non-survivor category. This categorization was instrumental in developing an inpatient mortality prediction model, indicating that data from deceased patients were integral to evaluating clinical outcomes. Such data can be utilized in CEA, particularly when the primary outcome is mortality or life-years saved.

Although studies show comorbidities increase length of stay and costs in sepsis patients, these were excluded here. Organ transplantation, injuries, and chronic diseases are linked to longer stays and higher costs. However, analyzing costs based on length of stay faces challenges due to external factors, varying outcomes, and hospital characteristics rather than disease factors, preventing comorbidity analysis.

An additional limitation that restricts the international generalizability of this paper is the potential variation in the prices of the two drugs (meropenem and ceftriaxone) across different countries.

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Conflict of Interest

The authors declare no conflicts of interest.

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