RESEARCH ARTICLE

Cost-effectiveness analysis of ceftriaxone and levofloxacin for therapy of urinary tract infection at Soebandi public hospital

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Abstract

Background: An ideal therapeutic option should be effective and have a low cost. The first-line therapy of urinary tract infection (UTI) includes cephalosporin and fluoroquinolone. **Objective:** To find out which antibiotic therapy is more cost-effective between ceftriaxone and levofloxacin using a cost-effectiveness analysis test. **Method:** The study was conducted retrospectively using medical records and patient direct medical cost data for 2019 and 2020. The records of 21 patients met the inclusion criteria. Data processing and decision-making were carried out using descriptive and inferential statistical analysis, average cost-effectiveness (ACER) calculations, and a cost-effectiveness grid. The outcome parameter used in a cost-effectiveness analysis was the percentage of effectiveness of empirical therapy. **Result:** The results showed that 61.9% of patients received ceftriaxone and 38.1% received levofloxacin. The average length of hospitalisation of UTI patients with levofloxacin therapy was shorter than those treated with ceftriaxone (four versus five days) with a *p*-value = 0.066. The average cost of ceftriaxone treatment was higher than that of levofloxacin (IDR 2,352,307 versus IDR 1,867,183). Based on statistical analysis carried out on each component of direct medical cost, the results were not significantly different between the cost of treatment with ceftriaxone or levofloxacin (*p* = 0.107). The percentage of effectiveness of empirical therapy using levofloxacin was higher than ceftriaxone (100% versus 90.5%). ACER value of total levofloxacin cost (IDR 18,672 per percentage effectiveness) has a lower value compared to ceftriaxone (IDR 26,000 per percentage effectiveness). **Conclusion:** Using the cost-effectiveness grid, levofloxacin is a more effective therapy, therefore the treatment of UTIs at Soebandi public hospital using levofloxacin are more cost-effective.

Introduction

Urinary Tract Infections (UTIs) are generally caused by the intestinal flora, 80 - 90% are non-compound UTIs and fewer than 50% of cases are community infections generally caused by *Escherichia coli* (Bader, Hawboldt & Brooks, 2010; Wells *et al.*, 2015). According to the Ministry of Health of the Republic of Indonesia (2014), the number of UTI sufferers in Indonesia is quite large, reaching 90 - 100 cases per 100,000 population per year. According to the European Association of Urology (2020), fluoroquinolone and cephalosporins are

antibiotics used for the therapy of non-complicated pyelonephritis. Empirical therapy of complicated UTIs can use antibiotics such as fluoroquinolones, aminopenicillin + beta-lactam inhibitors, cephalosporins, or aminoglycosides (EAU, 2020). The ideal therapy option should have good efficacy and an affordable cost, which helps policymakers to implement drug choices (Setiawan, Endarti & Suwantika, 2017).

Ceftriaxone and levofloxacin are the single antibiotics that have the largest percentage use at Soebandi public hospital, 31.1% and 15.6% respectively, with an average

duration of treatment of four and three days respectively. Based on these data, and judging from the length of hospitalisation, fluoroquinolone is more therapeutically effective. However, the percentage of levofloxacin use is still lower than that of ceftriaxone. Therefore, data on the effectiveness of the use of these antibiotics are needed for pharmacoeconomic testing to provide relevant data to policymakers to ensure effective treatments for UTI patients at Soebandi public hospital.

This study aims to determine which antibiotic therapy, ceftriaxone or levofloxacin, is more cost-effective in the treatment of UTIs at Soebandi public hospital based on cost-effectiveness analysis.

Methods

Design

This study was conducted using description and analytic research design at Soebandi public hospital, Jember, East Java, Indonesia. Data collection and analysis were conducted from May to June 2021. This study is a retrospective study using medical records and direct medical cost data of UTI patients in 2019 and 2020. The samples in this study were UTI patients in 2019 and 2020 who met the inclusion criteria. Inclusion criteria included inpatients diagnosed with UTI, patients receiving levofloxacin or ceftriaxone as single antibiotic therapy, patients aged over 18 years old, and complete patient medical records (patient identity, laboratory examination results, drug use data) as well as direct medical cost data. Data processing and decision-making were carried out using descriptive and inferential statistical analysis, average cost-effectiveness ratio (ACER) calculations, and a cost-effectiveness grid.

Assessment

The percentage of therapeutic effectiveness used as an outcome parameter for cost-effectiveness analysis was the total percentage of patients treated and given antibiotics for a maximum of five days, which was the upper limit value of the UTI empirical therapy guide. The data of the results of the analysis were presented quantitatively in the form of tables supported by textual narratives. Ethical approval to conduct the study was granted by the Ethics Committee of the Medical Research, Faculty of Dentistry, University of Jember (Number 1179/UN25.8/KEPK/DL/2021).

Results

The number of patients with UTI diagnoses in 2019 and 2020 at Soebandi public hospital was 76. Of these, only 21 patients met the inclusion criteria. Patient characteristics are shown in Table I. Results showed that the majority of patients were male (52.4%). Based on age characteristics, most patients (28.6%) were in the age range of 56 – 65 years. The most widely used type of antibiotic was ceftriaxone (61.9%). This study also showed that there were more UTI patients with comorbidities than patients without comorbidities; Most UTI patients had one comorbidity (57.3%). The effectiveness of therapy was measured using the parameters of the duration of hospitalisation (Table II).

Table I: Patients characteristics organised by empirical antibiotics treatment for UTI at Soebandi public hospital from 2019 to 2020 (n = 21)

Patients characteristics	Number	%
Gender		
Male	11	52.4
Female	10	47.6
Age		
19-25	2	9.5
26-35	4	19.1
36-45	3	14.2
46-55	4	19.1
56-65	6	28.6
>65	2	9.5
Antibiotic type		
Ceftriaxone iv	13	61.9
Levofloxacin iv	8	38.1
Comorbidity condition(s)		
Patient with no comorbidities	6	28.6
Patient with one comorbidity		
Diabetes Mellitus	2	9.5
Dyspepsia	2	9.5
Urosepsis	2	9.5
Hypokalemia	1	4.8
SBO	1	4.8
BPH	1	4.8
HHD	1	4.8
HHF	1	4.8
CKD	1	4.8
Patients with two comorbidities		
Diabetes Mellitus + Dyspepsia	2	9.5
Dyspepsia + Vulvovaginitis	1	4.8

SBO = *simple bowel obstruction*;
BPH = *benign prostatic hyperplasia*;
HHD = *hypertensive heart disease*;
HHF = *hypertensive heart failure*;
CKD = *chronic kidney disease*

Table II: Average length of stay between the two treatment groups

Empirical antibiotic type	Average length of stay (days) ± SD	*p*-value
Ceftriaxone iv	4.62 ± 0.71	0.066
Levofloxacin iv	3.75 ± 1.12	

SD = *Standard deviation*

The average length of hospitalisation of patients with levofloxacin therapy was shorter than those treated with ceftriaxone (four versus five days) with a value of *p* = 0.066. The average cost of ceftriaxone treatment was higher than that of levofloxacin (IDR 2,352,307 versus IDR 1,867,183, respectively). Based on statistical analysis carried out on each component of medical expenses, there was no significant difference between the cost of ceftriaxone treatment and levofloxacin (*p* = 0.107) (Table III). The percentage of effectiveness of empirical therapy using levofloxacin was higher when compared to that of ceftriaxone (100% versus 90.5%) (Table IV). ACER value of total levofloxacin cost (IDR 18,672 per percentage effectiveness) has a lower value compared to ceftriaxone (IDR 26,000 per percentage effectiveness) (Table IV). Using the cost-effectiveness grid, levofloxacin was more effective.

Table III: Direct medical cost distribution between the two treatment groups

Parameter	Levofloxacin iv (IDR)	Ceftriaxone iv (IDR)	*p*-value
Service cost	454,688	492,115	0.528*
Supporting examination cost	440,163	459,977	0.861*
Activation cost	349,625	396,192	0.382*
Accommodation cost	298,750	366,000	0.130+
Cost of supporting drugs and medical devices	251,059	479,859	0.089+
Antibiotic cost	72,899	53,455	0.124*
Total	1,867,183	2,352,307	0.107*

* = *Independent t test*
+ = *Mann Whitney Test*
IDR = *Indonesian Rupiah*

Table IV: ACER calculation of each antibiotic group

Empirical antibiotic type	Cost (C)	Effectiveness (E)	ACER (C/E)
Levofloxacin iv	IDR 1,867,183	100%	18,672
Ceftriaxone iv	IDR 2,352,307	90.47%	26,000

Discussion

The incidence of UTIs is generally more common in women than men for all age groups. This happens because, anatomically, women's urethras are shorter than men's; Women's urethra is only four centimetres long and is close to the anus which makes it more accessible to gram-negative bacillus bacteria to colonise (Baso, Perwitasari, & Risdiana, 2018). In older patients, several risk factors can increase the incidence of UTIs, such as decreased cognitive abilities which result in impaired self-care efforts, and non-optimal bladder emptying (urine flow speed <10 mL/s and remaining urine in the bladder >100 mL/s), which causes the bladder to always hold urine which can act as a medium for bacterial growth (Torayraju, 2015). In men over the age of 50, prostate hypertrophy with partial obstruction becomes the main supporting factor in increasing the risk of UTIs. Risk factors that are more commonly observed in elderly men are cognitive impairment, faecal or urinary incontinence, and catheter use (Brusch, 2020). In elderly women, oestrogen deficiency occurs and causes the genitalia area to become drier. As a result, it is easier to become infected, and vaginal acidity is reduced. As the general protection of the mucosal area is reduced, bacteria find it easier to colonise (Torayraju, 2015).

The use of ceftriaxone as an empirical therapy is because ceftriaxone has a wide spectrum of activity against gram-negative bacteria that commonly cause UTIs (Wells *et al.*, 2015). According to reports, there were 16 cases of gram-negative bacterial infections and two cases of Gram-positive bacterial infections in Soebandi Hospital from 2014 to 2017 (Syahputra, Agustina & Wahyudi, 2018). Ceftriaxone is an antibiotic of the broad-spectrum cephalosporin group as a therapy for pyelonephritis UTIs, especially for patients who need hospitalisation (Kang *et al.*, 2018). The top three types of comorbidities experienced by patients in this study were diabetes mellitus, dyspepsia, and urosepsis. A cohort study comparing the incidence of infection in type 2 diabetic patients and non-diabetic patients conducted in the United Kingdom by Hine and colleagues (2017) showed that UTIs had a strong positive association with type 2 diabetes mellitus. Hyperglycemia has been shown to interfere with several mechanisms of the immune system (Jafar, Edriss & Nugent, 2016). In the case of UTIs, there is a neuropathic disorder of bladder emptying as well as the need for a catheter, and glycosuria caused by the new sodium-glucose cotransporter-2 inhibitor drug (SGLT2), which can contribute to the incidence of infection (Hine *et al.*, 2017).

Length of stay in the hospital is an important indicator of medical services and can be used to assess the

efficiency of hospital management, the quality of patient services, and functional evaluation. Shorter hospitalisation periods reduce the burden of medical costs and increase bed turnover rates, which in turn increases hospital profit margins while lowering overall social costs (Baek *et al.*, 2018). In general, UTIs without comorbidities improve after three days of antibiotic therapy. The length of hospitalisation of the patient can be influenced by several factors, including the severity of the disease, the side effects of drugs, and the possibility of other drugs being taken by the patient before being hospitalised (Susono & Galistiani, 2014).

The component of direct medical costs at Soebandi Public Hospital includes service cost, supporting examination cost, activation cost, accommodation cost, antibiotic cost, and the cost of supporting drugs and medical devices. The highest average cost in both groups of therapies is the cost of services. In the levofloxacin group, the average service fee is IDR 454,688 while in ceftriaxone it is IDR 492,115. The component of direct medical costs that do not differ significantly can be influenced by a relatively small number of samples, as well as the determination of the number of treatment rates that have been set by Badan Penyelenggara Jaminan Sosial Kesehatan (translated as Social Security Agency of Health (BPJS)) in the Indonesia Case Based Groups (INA-CBG) tariff. The results of simulations carried out by Filho and colleagues (2013) show that the larger the sample size, the higher the probability of detecting statistical significance. According to the Regulation of the Minister of Health Number 69 of 2013, the calculation of INA-CBG tariffs is based on costing data and coding data from the final diagnosis and actions that are the output of services using International Classification of Diseases (ICD) 10 and ICD-9 references. The amount of costs set is influenced by several aspects of the INA-CBG system, including: the main diagnosis, secondary diagnosis in the form of accompanying or complicating, severity, the form of intervention, and variations in the age of the patient (Ananta, 2016). In this study, diagnosis and severity were factors that triggered the absence of significant differences in the components of patient treatment costs. The diagnosis of all patients in this study was a UTI (ICD code N.39/INA-CBGs code N-4-12) with mild and moderate severity. It is this similarity that makes patients have similar INA-CBGs codes so that the rates imposed on patients do not differ significantly.

The outcome parameter used for cost-effectiveness analysis is the percentage of the effectiveness of empirical therapy. According to the guidelines (EAU, 2022), empirical therapy of UTIs should last only three to five days. In this study, the therapy was declared effective if the patient was treated for a maximum of five days. Patients who received levofloxacin showed higher therapeutic effectiveness than those who got ceftriaxone. In the calculation of ACER values, patients who received levofloxacin had lower values compared to those who received ceftriaxone. Based on the analysis of ACER values, it can be stated that levofloxacin therapy is more cost-effective compared to ceftriaxone therapy. Cost-effectiveness analysis was also carried out using the cost-effectiveness grid. The results show that levofloxacin was more cost-effective under these calculations than ceftriaxone i.e. levofloxacin has higher effectiveness at a lower cost (Tri Murti Andayani, 2013).

Fluoroquinolones are recommended and have a high level of evidence (IA) in case of non-compound pyelonephritis if the infection-causing bacteria show sensitivity to antibiotics during culture tests. The use of levofloxacin 750 mg for five days showed a clinical cure rate of 86.2%. The effectiveness of levofloxacin is also seen from the pharmacokinetic profile. Levofloxacin is rapidly absorbed and widely distributed in the body since its bioavailability is 99%. Therefore, intravenous and oral preparations of levofloxacin can be used interchangeably. Levofloxacin clearance is mainly through the renal route (87%) (Podder & Sadiq, 2022). Levofloxacin bond in plasma proteins is low (≤ 38%). Levofloxacin is distributed throughout the body and its concentration in other tissues (e.g. fluid of the epithelial layer, alveolar cells or macrophages, paranasal sinus mucosa, and urine) may exceed the concentration in plasma two to four hours after administration (Bientinesi, Murri & Sacco, 2020).

Conclusion

The average length of hospitalisation of patients with levofloxacin therapy is shorter than ceftriaxone therapy, however, there is no significant difference in the length of hospitalisation for the two therapeutic options. The average cost of treatment of ceftriaxone is higher compared to levofloxacin. On average the total cost of treatment showed no significant difference between the treatment of ceftriaxone and levofloxacin. The percentage of effectiveness of empirical therapy using levofloxacin is higher than ceftriaxone therapy. ACER values at the average total cost of levofloxacin have lower values compared to ceftriaxone. In the interpretation using the cost-effectiveness grid, levofloxacin is the more beneficial, so it can be concluded that in the treatment of UTIs at Soebandi public hospital levofloxacin use is more cost-effective**.**

Acknowledgement

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