Defined Daily Dose and Cost of Therapy of Empirical Ceftriaxone Pre- and Post-Antimicrobial Stewardship Program Model Implementation in Sepsis Patients in Dr. Hasan Sadikin General Hospital Bandung, Indonesia

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Abstract

Objective: Antibiotic resistance requires substantial responses through two mechanisms: new antibiotic development and smart antibiotic use. Antibiotic Stewardship Program (ASP) is one of the responses that reduce the overall antibiotics use and prevent the overuse of antibiotics to avoid antibiotic resistance. The purpose of this study was to assess the difference in defined daily dose (DDD) and the cost of therapy (COT) for empirical ceftriaxone therapy in sepsis patients pre- and post-ASP model implementation in Dr. Hasan Sadikin General Hospital, Bandung.

Methods: A pre- and post-intervention quasi-experimental study on ASP model implementation in empirical ceftriaxone therapy provided to sepsis patients treated in the intensive or semi-intensive care units was performed from December 2015 to July 2016 using the Mann Whitney test and t-test. The DDD was calculated as DDD/100 patient-days, while the COT was calculated as the COT/patient-day. The ASP model intervention implemented in these units applied 2 main strategies: ceftriaxone use restriction and ceftriaxone therapy duration audit.

Results: Participants of this study consisted of 112 sepsis subjects (n=112) with 55 subjects in the pre-ASP group and 57 subjects in the post-ASP group. The mean DDD/100 patient-days in the post-ASP subject was lower than that of the pre-ASP (16.3±4.3 and 45.8±16.8; p=0.018). The median COT/patient-days in post-ASP subject was IDR 42,000 (IDR 14.000–42.000), which was lower than that of the pre-ASP group of IDR 84.000 (IDR 28.000–420.000, p=0.001)

Conclusions: The differences in the DDD/100 patient-day and COT/patient-day values between the pre-ASP and post-ASP are significant. The ASP model applied in Dr. Hasan Sadikin General Hospital, Bandung leads to a smart use of ceftriaxone and reduces costs for the empiric ceftriaxone therapy in sepsis patien

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Introduction

Antimicrobial resistance associated with antibiotic uses, it is predicted of 50% or more antibiotic uses in hospital were inappropriate.[1] Signs and symptoms of infection in sepsis are insignificant due to immunity changes, thus increases worries of death if broad spectrum antibiotic therapy were not given early in sepsis patients. Therefore, broad spectrum antibiotic was overused, such as ceftriaxone, and will increase pathogenic bacterial resistance in sepsis patients.[2] Pradipta *et al*. show that ceftriaxone is one of six most common used

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antibiotic in hospital with resistance value more than 50% in sepsis patients in Bandung.[3]

Antimicrobial stewardship program (ASP) is a coordinate intervention based programs to increase and measure appropriate antibiotic use, by promoting optimal antibiotic choices, including doses, duration and route of therapy.[4] This programs aims to measure hospital antibiotic use, antibiotic resistance, and clinical outcomes.[5] Some measurement of antibiotic uses are defined daily dose (DDD), days of therapy (DOT), and cost of therapy (COT) per 100 patient per day.[6]

ASP model RSUP dr. Hasan Sadikin, are expected to reduce uses and cost of ceftriaxone.[5] This study enrolled to find differences value of ceftriaxone use as empiric therapy, DDD/100 patient-day and COT/ patient-day pre and post ASP Model RSUP dr. Hasan Sadikin in sepsis at intensive and semi-intensive care unit.[7] Sepsis with various source of infection, will increase risk of mortality.[8] Infection occurs in 51% of intensive care unit (ICU) patients, in which 71% were bacterial infection and treated with antibiotics.[9] Pathophysiological changes in critical illness causes alternation of drugs pharmacokinetic, especially hydrophilic antibiotics. These pathophysiological changes will make decision making difficult to determine the dosage and selection of antibiotics. Both the doses and class of antibiotics are important parameters of antibiotic therapy in septic patients. Antibiotic resistance requiring substantial response through two mechanisms: new antibiotic development and smart antibiotic use. This requires substantial changes, by implementing Antibiotic Stewardship Programs (ASP) that reduce overall antibiotics use and prevents overuse for reduce antibiotic resistance.[10]

Methods

Sepsis subject were chosen from medical records with ceftriaxone empirical therapy. The Ethical Clearance number LB.04.01/A05/ EC/262/VIII/2016 from Ethical Committee General Hospital Dr. Hasan Sadikin Bandung. Subject criteria for this study are sepsis patients, aged more than 15 years old and diagnosed with presumptive criteria of sepsis based on Surviving Sepsis Campaign 2012 and not with chronic illness nor comorbidity.[8] Subjects pre ASP were chosen from medical records, since December 2015 until March 2016. Sepsis Subjects post ASP with intervention by ASP Model Dr. Hasan Sadikin General Hospital, Bandung were chosen based on arrival of sepsis patients within study period (*consecutive sampling from admissions*) during of April until July 2016 in intensive and semi-intensive care unit.

This is a quasi-experimental study with unpaired numerical, comparative analysis by using Mann Whitney and t tests, the number of subjects in each group of at least 55 subjects in the pre-ASP and post ASP models.

The ASP model intervention with 2 main strategies, restrictions on ceftriaxone use and an audit for the duration of ceftriaxone therapy that has been given. Measurement method of quantitative ceftriaxone uses are defined daily dose (DDD) per 100 patient per day as recommended by the World Health Organization (WHO). Calculation of DDD/100 patients-day using this formula: DDD = DDD(WHO)/100 patients-day. The direct cost of therapy (COT) ceftriaxone: ceftriaxone daily dose multiplied by the number of days ceftriaxone therapy.[6,7]

Results

Sepsis subjects (n=112) in intensive and semi-intensive care unit RSUP dr. Hasan Sadikin General Hospital, Bandung from December 2015 to July 2016 (Fig. 1).

Sepsis subjects in both groups with an average age under 60 years and more in men. Source of infection as a cause of sepsis, especially in the lower respiratory tract and digestive tract. The treatment of patients with sepsis was found to be more in the ICU room than the high care room, the length of stay in the post ASP group was shorter than that of the pre-ASP group. Clinical features

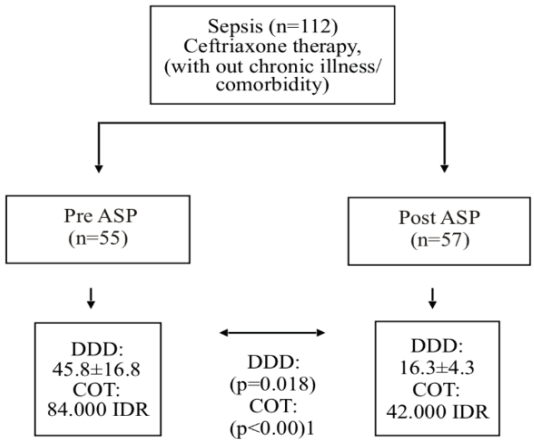

Fig. 1 Study result (Sepsis Patients, n=112)

Table 1 Subject Characteristics

Characteristics	PreASP (n=55)	Post ASP (n=57)	p-value
Age (years old)	44±17	43 ± 16	0.844[a]
Sex			
Male	29 (52.7)	28 (49.1)	0.703[c]
Female	26 (47.3)	29 (50.6)	
Source of infection			
Intraabdominal	23 (41.8)	20 (35.1)	
Pulmonary	21 (38.2)	20 (35.1)	0.543[c]
Skin and Soft tissue	9 (16.4)	16 (28.0)	
Genitourinary	2 (3.6)	1 (1.8)	
Ward			
ICU	28 (50.9)	58 (51.7)	
HCU Kemuning	21 (38.2)	36 (32.1)	0.371[c]
MIC	4 (3.7)	11(9.8)	
Flamboyan	2 (3.6)	7 (6.2)	
Length of Stay	20 (5-57)	16 (3-72)	0.071[b]
Vital signs			
GCS<10	20 (36.3)	12 (21.1)	0.089[c]
Temperature (^{0}C)	37.8 (34-40.2)	37.8 (35.2-40.6)	0.493[b]
Heart rate (beats per minute)	111 (56-160)	110 (100-165)	0.726[b]
Respiratory rate (breaths per minute)	28 (18-47)	28 (16-52)	0.724[b]
Systolic Blood Pressure (mmHg)	113 (56-160)	119 (88-173)	0.346[b]
Diastolic Blood Pressure (mmHg)	70 (34-90)	70 (52-90)	0.541[b]
Laboratory Values			
Leukocyte (10^3/mm^3)	17.2 (2.2-53.9)	17.1 (1.8-42.6)	0.710[b]
Thrombocyte (10^3/mm$^{3)}$	256 (8-950)	260 (52-981)	0.707[b]
NLCR	9 ± 9.2	11 ± 10.7	0.743[a]
CRP (mg/dL)	51.3 (1.5-282.6)	80.0 (4.5-408.4)	0.526[b]
CRP>50 mg/dL	5 (50)	6 (54.5)	0.758[c]
PaCO2 (mmHg)	31.6 (14.7-99.0)	29.0 (16.5-87.0)	0.252[b]
Creatinine (mg/dL)	1.0 (0.3-6.3)	0.9 (0.3-5.6)	0.974[b]
INR	1.0 (0.8-3.7)	1.0 (0.8-2.3)	0.837[b]
aPTT (seconds)	25.9 (15.3-114.7)	27.8 (18.2-50.3)	0.153[b]
Total Bilirubin (mg/dL)	0.6 (0.1-24.9)	0.7 (0.3-30.8)	0.622[b]
Lactate (mmol/L)	1.8 (0.6-9.8)	3.1 (0.4-13.8)	**0.047[b]***
Duration of Ceftriaxone use as empirical treatment			
≤72 Hours	19 (34.5)	57 (100.0)	**<0.001[c]***
>72 Hours	36 (65.5)	0 (0.0)	

Note: Data presented as n (%), mean± SD, *Median* (range), analysis with [d]t-test, [b]Mann Whitney, and [c]Chi Square test, *significance

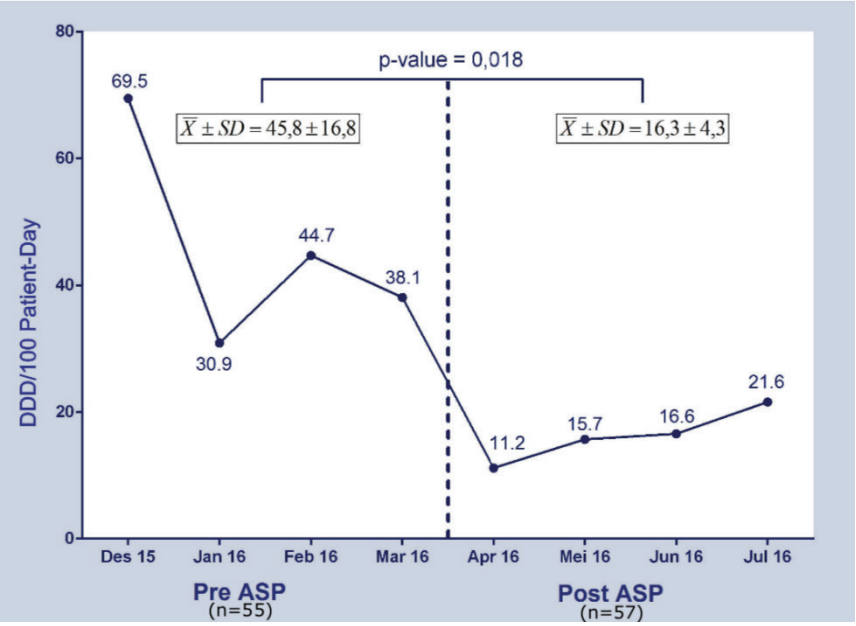

Fig. 2 The DDD/100 Patient-day of Ceftriaxone Empirical Treatment Pre and Post ASP. (n=112)

of sepsis subjects in both groups were in accordance with SSC 2012.[8] The duration of using ceftriaxone as an empirical treatment was less than 72 hours in post ASP group that significantly different compared to the pre-ASP group. The ASP model intervention, as the main strategy in limiting the use of ceftriaxone as an empirical therapy, is aimed at empiric antibiotic therapy not more than 72 hours.[11] Consideration for substituting for definitive therapy is a clinical decision policy that refers to the clinical condition of the patient and the results of bacterial culture examination from the source of infection as a cause of sepsis.[12] (Table 1).

Mean of DDD/100 patient-day of ceftriaxone use as empirical treatment in post ASP was lower than those in pre-ASP (16.3±4.3 and 45.8±16.8, consecutively) with p=0.018. (Figure 2).

Median value of COT/patient-day of ceftriaxone use as empirical treatment post ASP were 42.000 IDR (14.000-42.000 IDR), lower than pre-ASP which were 84.000 IDR (28.000-420.000 IDR), with p-value <0.001 (Table 2).

Discussion

All subject with sepsis, also met with New Definition of Sepsis (Sepsis 3), quick SOFA was 3, in all subject as well, with not fully alert, tachycardia and tachypnoea. Looking in Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA), all subject with GCS below 10, that means all subject with SOFA score at least 3, which relevant to sepsis patents. Lactate level were significant high in post ASP (p=0.047) also like sepsis patients pattern.[13] According to the new Sepsis Bundle as in Sepsis Bundle 1 Hour, if initial lactate over 2 mmol/L, must be repeated measure

Table 2 COT/Patient-Day Value of Ceftriaxone Empirical Treatment Pre and Post ASP.

COT	Pre-ASP (n=55) (IDR)	Post-ASP (n=57) (IDR)	Difference (IDR) (95%CI)	p-Value
COT/patient-day	84.000 (28.000 –420.000)	42.000 (14.000 – 42.000)	42.000 (28.000 – 70.000)	<0.001

Note: Data presented in median, analysis using Mann Whitney test.

lactate level after initial fluid resuscitation for stabilizing hemodynamic parameters.[14]

All sepsis subject, with various causes of infections, like intra-abdominal, pulmonary, urinary tract, skin and soft tissue infections. Markers of infection were reactive in all subject, like Leukocytosis and CRP over 50 mg/dl. Blood cultures before antibiotic treatment were done 50.9% in post ASP, in pre-ASP blood cultures were done only in 43.7%. In post ASP, diagnosis for sepsis is more accurately, by perform blood culture for finding the cause of bacterial pathogen this result is similar to Robertson C L and Haddad A. M., for appropriate antibiotic treatment base on culture result and antibiotic susceptibility test.[8]

All sepsis subject treated with empiric ceftriaxone antibiotic, in post ASP, empiric ceftriaxone use was 0% for over 72 hours and 65.5% in pre-ASP ($p<0.001$). ASP Model Dr. Hasan Sadikin General Hospital, Bandung, could guide prudent empiric ceftriaxone use in this study.[11] The most common method used to accurately reflect antimicrobial usage is the defined daily dose (DDD) promoted by the World Health Organization (WHO). WHO defines DDD as "the assumed average maintenance dose per day for a drug used for its main indication in adults" To estimate the total number of days of antimicrobial therapy, healthcare personnel should divide the total grams of each antimicrobial used for a given period of time by the WHO-defined DDD for the individual antimicrobials.[15]

Calculation of ceftriaxone DDD/100 patients-day shows, that ceftriaxone DDD/100 patients-day, in post ASP were lower than those pre-ASP (16.3±4.3 and 45.8±16.8, $p=0.018$). These results are similar to Cairn *et al*., Lin *et al*., studies, in which show decrease of DDD/100 patients-day after ASP intervention.[16,17]

Value of ceftriaxone COT/patient-day in post ASP were lower than those in pre-ASP [consecutively IDR 42.000 (IDR 14.000–42.000) and IDR 84.000 (IDR 28.000–420.000), $p<0.001$]. The result is similar to the previous studies by Lin *et al*.,[20] which showed that there is reduction of COT/patient-day after ASP intervention. The difference of COT value in pre-ASP and post ASP were IDR 42.000 per patient per day. It describes that there is daily antibiotic cost savings up to IDR 42.000 per patient after intervention ASP Model Dr. Hasan Sadikin General Hospital, Bandung.

Consistence with JCI, ASP's can consider using a hybrid program that implements both approaches. Formulary restriction and preauthorization may be better at saving money and optimizing doses, whereas a prospective audit and feedback program addresses resistance problems, and improves overall antimicrobial use, like ASP Model Dr. Hasan Sadikin General Hospital, Bandung.[18]

Limitations in this study, this study must be continued with the design of RCT study and conduct with blood culture results or antibiotic susceptibility tests to determine patterns of antibiotic resistance, which can be used for optimal definitive antibiotic treatment and outcomes in sepsis patients.

Differences DDD/100 patient-day and COT/patient-day value in pre-ASP and post ASP are significant. ASP model General Hospital Dr. Hasan Sadikin, Bandung can achieve smart use and improve cost saving in empiric ceftriaxone therapy in sepsis patients. Restrictions on the use of ceftriaxone for empirical therapy are intended as not to increase the resistance of pathogenic bacteria to ceftriaxone and as a prevention of over use.

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