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THE OUTCOME OF ANTIBIOTIC THERAPY AMONG CHILDREN WITH SEVERE COMMUNITY ACQUIRED PNEUMONIA

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Background: The effect of human immunodeficiency virus (HIV) status on the evolution of community acquired pneumonia (CAP) is still controversial. There are controversies regarding antibiotic treatment outcome of CAP in HIV infected children. **Objective:** The aim of this study was to investigate possible differences in hospital outcomes, with compared the outcome of the treatment in severe CAP among HIV infected and HIV uninfected children which had an empiric antibiotic therapy. **Methods:** A case control study of 80 patients with severe CAP in Department of Child Health, Sanglah General Hospital, Bali-Indonesia. We evaluated clinical features for seeing the effectiveness of the antibiotic therapy according to Department of Child Health, Sanglah General Hospital's clinical pathway for severe pneumonia between HIV infected and HIV uninfected patients. **Results:** 58% patients in failure treatment and 45% patients in favorable treatment were HIV infected. There were similar characteristics from both groups, except malnutrition condition was statistically significant contribute the outcome (OR 2.87 (95% CI 1.098 to 7.500, p= 0.031). There was no significantly statistic difference of the outcome in HIV infected as compared to HIV uninfected patients with severe CAP (OR 1.65 (95% CI 0.683 to 4.002, p= 0.263). **Conclusion:** HIV infection was not gave an effect on the outcome of severe CAP patients which had an antibiotic therapy based on Department of Child Health, Sanglah General Hospital's clinical pathway for severe pneumonia.

Keywords: Community acquired pneumonia; HIV infection; Antibiotic; Outcome; Children

INTRODUCTION

Pneumonia is the infections causing the largest proportion of deaths, and there has been no reduction in mortality rates associated with these infections in recent decades. Community Acquired Pneumonia (CAP) is a common cause of morbidity and mortality in developing countries.[1-3]The magnitude of this problem has been exacerbated by the current Human Immunodeficiency Virus (HIV) epidemic in developing countries, because pneumonia has emerged as one of the most common causes of illness, hospitalization, and mortality in HIV-infected children.[4]The increase prevalence of HIV in children in developing country contributes to the increase of CAP prevalence.[5] There are controversies regarding treatment outcome of CAP in HIV infected children. For instance, some studies shown that HIV infection negatively leads to fatal outcome in patients with CAP is still uncertain, [1,3,5,6] justifying at times the exclusion of HIV patients from trials on CAP.[7] In spite of the proven efficacy of empirical antibiotic treatment on CAP in people with HIV,[8-10] the management of the condition in Social Security Administration (SSA) is still compromised by the lack of bacteriological investigations. Moreover, the fear of pejorative evolution often leads to frequent hospitalization of CAP patients with HIV, even in the absence of classical clinical signs of severity of the disease.[10]The incidence of treatment failure in CAP has been estimated to be 11% and the generally accepted period of time considered for failure is 72 hours. [7]

The independent risk factors of treatment failure associated were multi-lobar CAP, cavitation on chest radiograph, pleural effusion, HIV status and liver disease.[7]In last study, the effects of HIV infection of CAP 15 years ago, reported frequent bacteremia in patients with HIV.[1] In the context of the growing population of individuals with HIV infection in SSA in general, the current report aims to update the knowledge on the potential effects of HIV infection on CAP by investigating differences if any in the clinical presentation and in hospital outcomes of CAP patients with and without HIV infection children. Although many epidemiological and prognostic studies of CAP have been published, there is very little information about outcome from

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antibiotic treatment in CAP especially in children with HIV infected. Studies are needed to identify patients for evaluating the treatmentand to design strategies or plan specific health care and/or treatment for these patients. Moreover, treatment failure increases the need for microbiological and diagnostic tests with the resulting longer hospital stay and increased costs. The aim of this study was to investigate possible differences in hospital outcomes, with compared the clinical response in severe CAP among children with HIV infected and HIV uninfected children which had an empiric antibiotic therapy.

METHODS

This study was a case control study in Department of Child Health, Medical School, Udayana University, Sanglah General Hospital, Bali-Indonesia. Recruitment for this study was restricted to patients aged between a month until 12 years old, with retrospective data from medical record of all children whose diagnosed severe CAP with HIV infected and HIV uninfected during January 2011 until June 2013. Patient with data from the medical record did not complete, patient with danger signs of very severe pneumonia, severe malnutrition, chronic cardiopulmonary conditions, asthma, or penicillin allergies, patient did not finished the therapy for leaving hospital with their own will, children are referred patient from other hospital, and have been hospitalized in 14 days before admitted were excluded.

The subject of this study was recruited by applying consecutive sampling. The samples are those who fulfilled the inclusion criteria. For all eligible patients, data of age, sex, admission date, results of HIV status and diagnosis were taking from medical record. Biological data recorded, included the complete blood count, blood culture, C-reactive protein, history of HIV rapid test results. We put the severe CAP with failure treatment in case group and the severe CAP with favourable treatment as a control group. The evolution data included clinical signs and symptoms included the cough, fever, tachypnoethose relating to treatment failure at day three following inception, treatment success.[10]Wedivided subject into two groups, CAP with favorable treatment and CAP with failure treatment. The study protocol was approved by the institutional board of the Department of Child Health, School of Medicine, Udayana University Sanglah Hospital, Bali-Indonesia.

All the patients data of age, sex, admission date, a clinical examination, nutritional status, chest X-ray, biological workup comprising a complete blood count, blood culture, C-reactive protein, and HIV status. Severe CAP was diagnosed by pediatrician from clinical signs and symptoms included a cough, fever (with fever defined as a temperature ≥38°C) and tachypnoe to World Health Organization (WHO) defined.[7] Nutrition status was defines to World Health Organization (WHO) Anthrocriteria for well nourish was a weight for height between -2SD until +2SD and malnutrition was a weight for height less the same -2SD.[8] Anemia defines with hemoglobin count less than 10g/dL for children age under 1 year, less than 11 g/dL for children 1-6 years old, and less than 12 g/dL for children age more than ^ years old according to WHO. Leucosytosis defines with leucosyt more than $12x10^3/\mu L$, trombositopenia defines with trombosit less than $150x10^3/\mu L$, CRP increased defines with CRP more than 5 mg/L. Upon admission to this hospital, routine evaluation of patients suspected of having severe CAP received included biological workup comprising a complete blood count, C-reactive protein and bacteriological investigations to isolate the microbial etiology were done in Sanglah Hospital Laboratory. Chest X-rays was taken and read by Sanglah Hospital radiologist.HIV infected patient was already diagnosed by pediatrician from positive rapid test history. On admission to the hospital, patients were treated with antibiotics empirically and treatment was based on Department of Child Health, Sanglah General Hospital's clinical pathway for severe pneumonia. Treatment failure on the third day was based on the no abatement of the fever and worsening of chest signs, favorable response to treatment at this same time point was defined by the regression of lower respiratory tract infection signs and particularly thermal defervescence or body temperature normalization.[10]

Statistical Analysis

Data were analyzed using supported computer program. Group comparison was assesed used Pearson $\chi 2$ and the odds ratio with a 95% confidence interval was calculated. We used a *p* value <0.05 to statistically significant results.

RESULTS

A total of 93 children with severe CAP were entered into the study, of these, 6children with severe malnutrition, 2 children were did not finished the therapy for leaving hospital with their own will and 5 children are referred patient from other hospital. Therefore 80children with severe CAP were enrolled in this study. The main demographic characteristics were summarized in **Table 1.** Among them 40 were severe CAP with favorable treatment. The medianage of patients was 8.5 (IQR 13) month in a severe CAP with favorable treatment group and 19 (IQR 21) months in failure treatment groups. C-reactive protein in the severe CAP with favorable treatment group were lower than failure treatment patients, 17.1 (IQR 11.6) and 25.3 (IQR 25.5), respectively. In contrast, the leucocytes count and hemoglobin in favorable

treatment group were higher than those in failure treatment group

Table 1
Characteristics of subjects in severe CAP with failure and favorable treatment

Characteristics	Severe CAP with failure treatment (n = 40)	Severe CAP with favorable treatment (n = 40)
Sex,n (%)		
Boys	25(63)	21(53)
Age, median (IQR) months	8.5 (13)	19 (21)
Nutrition,n (%)		
Well-nourished	13(33)	24(60)
Malnutrition	27(68)	16(40)
Hematologic features		
Leucocytes count, mean (SD) mm^3	14.82 (6.6)	15.23 (4.7)
Hemoglobin, mean (SD) g/dL	10.2 (1.6)	10.74 (1.8)
Platelet count, mean (SD) mm^3	356.48 (127.4)	345.05 (125.1)
C-Reactive Protein, median,(IQR) mg/L	25.3 (25.5)	17.1 (11.6)
Blood Culture, n (%)		
Staphylococcus aureus	7 (18)	4 (10)
Pseudomonas aeruginosa	2(5)	-
Staphylococcus epidermidys	3 (8)	1(3)

The pathogens involved which etiologic diagnosis could be made within 5 up to 7 days are listed in Table 1. Positive blood culture was higher in group severe CAP with failure treatment. *Staphylococcus Aureus* was the most frequently isolated pathogen, followed by *Staphylococcus epidermidys* and *Pseudomonas aeruginosa*. Multivariate logistic regression analysis was carried out after adjustment of gender, hemoglobin, trombosit, leucosyte count and CRP, we found no statictically of mortality between two groups. We found that malnutrition condition was significant statistically of failure treatment on CAP in HIV patients shown in Table 2 (OR 2.87 (95% CI 1.098 to 7.500, p= 0.031).

DISCUSSION

In this study we demonstrated HIV infection and HIV uninfected among hospitalized child patients with CAP. A high HIV seroprevalence among patients with acute respiratory illness was already reported in Burundi (54%) and Tanzania (74%). These data indicate a high HIV seroprevalence rate among the general population of the other countries in Central and East Africa.[11,12] The CD4 lymphocyte counts of the HIV infected patients in this study were almost equally distributed less than 32%, whereas they were clustered in the group with CD4 less than 20% in a previous study of US patients.[10]

Table 2
Multivariate analysis of variable contributing to failure treatment of severe CAP

Characteristics	OR	95%CI	P value
Boys	0.654	0.249 to 1.718	0.389
Malnutrition	2.87	1.098 to 7.500	0.031
Anemia	1.043	0.304 to 3.577	0.578
Trombositopenia	0.733	0.042 to 12.788	0.831
Leucosytosis	0.931	0.191 to 4.547	0.931
CRP Increased	0.278	0.016 to 4.703	0.375

There were 23 (58%) HIV infected patients and 17 (42%) HIV uninfected patients with failure treatment and 18 (45%) HIV infected patients and 22 (55%) HIV uninfected with favorable treatment were in severe CAP. Not significantly rate of treatment failure was recorded in HIV infected as compared to HIV uninfected patients hospitalized with severe CAP (OR 1.65 (95% CI 0.683 to 4.002), P 0.263) shown in Table 3**.**

Table 3
Association between HIV status and the outcome to antibiotic therapy among children with clinical response severe CAP

HIV status	Clinical response of Severe CAP (n =40)		OR	95% CI	*p*
	failure treatment	favorable treatment			
infected, n (%)	23 (58)	18 (45)	1.65	0.683 to 4.002	0.263
uninfected, n (%)	17 (42)	22 (55)			

Among bacterial pathogens identified in HIV infected patients, we found not only *Staphylo coccus aureus*, but also *Pseudomonasaeruginosa*, although only a few of these strains had been identified as pathogens in previous studies in Africa.[9,10] Distribution of bacterial etiology for CAP among HIV infected persons were similar to those in the US.[9]The mean CD4 counts among HIV infected patients with CAP due to *S. aureus*were much lower than those due to major bacterial pathogens such as *S.pneumonia and s. epidermidys*. These data support the view that *S. aureus*is a causative pathogen of pneumonia in HIV infected persons with an advanced stage of immunosuppressant.

Recent studies indicated the successful treatment by shortterm intravenous beta lactam antibiotics prior to an oral switch for hospitalized patient with uncomplicated CAP.[10] In India,

investigators reported that all patients with CAP responded to one week of intravenous penicillin followed by oral antibiotics, with total therapy duration of 10 days. No study, however, has evaluated the usefulness of short term intravenousempirical antibiotic therapy for CAP in HIV infected individuals, especially in developing countries. In this study, nosignificantly rate of treatment intravenous empirical antibiotics failure was recorded in HIV infected as compared to HIV uninfected patients hospitalized with severe CAP. The present data support the usefulness of short term intravenousempirical antibiotic therapy for patients with severe CAP both in HIV infected and HIV uninfected patients. Treatment failures in cases of severe CAP maybe due to penicillin-resistant bacteria pathogens and due to unknown etiology, especially in HIV infected patients, indicate that careful etiologic diagnosis and targeted antimicrobial treatment is important. Further investigation of diagnostic etiologies and clinical effectiveness of short term intravenous empirical antibiotic therapy prior to an oral switch is required in order to provide proper guidelines for treatment of CAP in developing countries where HIV infection is common.

Human immunodeficiency virus, opportunistic infection, and nutrition are intimately linked. HIV infection can lead to malnutrition, while poor diet can in turn speed the infection's progress and favorable treatment.[11] In our study, in multivariate analyzed we found that malnutrition contribute the outcome on severe CAP in HIV patients.

Some limitations of this study was absence of history every patient of antibiotics therapy, ARV used and HIV viral load. Clinical features follow up for the entire HIV infected patient and HIV uninfected whose being hospitalized with severe CAP maybe needed for the next research.

In conclusion, HIV infection was not gave an effect on the outcome of severe CAP patients which had an antibiotic therapy based on Department of Child Health, Sanglah Hospital's clinical pathway for severe pneumonia.

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