Laporan Hasil Penelitian

CD4 T-LYMPHOCYTE CELL COUNTS AND PNEUMONIA IN HIV-INFECTED CHILDREN

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ABSTRACT

Background : Pneumonia is a major cause of morbidity and the most common cause of mortality in infants and children who are infected with *Human Immunodeficiency Virus*(HIV). For HIV-infected children, the risk for developing pneumonia has been closely related to an individual's having a lower CD4 T-lymphocyte cell count.***Objective:***Toevaluate for an association between CD4 T-lymphocyte cell count and pneumonia in HIV-infected children. ***Methods*** : A cross sectional study was conducted among all children diagnosed with and without pneumonia who had HIV at Adam Malik Hospital, Medan. Data were taken from patients' medical records between January 2008 to December 2015. We studied demographic, clinical, radiological and CD4 T-lymphocyte cell counts on admission, as well as mortality outcomes. ***Results :*** A total of 174 HIV-infected children were included in this study. Pneumonia was found in 47 children with 39 months as the median age of onset. The mean difference in CD4 levels was 0.912cells/mm^3 units (95% CI to -5.79 to 7.62) with higher mean in the pneumonia group than in the non-pneumonia group, but no significant difference. In addition, no significant association were found between nutritional status and incidence of pneumonia [OR 1,050; 95% CI 0,537 to 2,053); P = 0.886) or between immunodeficiency status and pneumonia, [OR 0.986;(95% CI 0,25 to 3.885);P= 0,984]. The common opportunistic infection in our subjects besides pneumonia were diarrhea, oral candidiasis and pulmonary TB, or some combination there of. Severe malnutrition was also present in some subjects. ***Conclusions :*** There is no significant association between CD4 T-lymphocyte cell count and pneumonia in HIV-infected children.

Key words **:** CD4, HIV, pneumonia, children
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ABSTRAK

Latar Belakang : Pneumonia adalah penyebab utama morbiditas dan penyebab kematian paling umum pada bayi dan anak-anak yang terinfeksi *Human Immunodeficiency Virus* (HIV). Pada anak yang terinfeksi HIV, risiko terkena pneumonia terkait erat dengan jumlah sel T CD4-limfosit yang lebih rendah. **Tujuan :** Mengevaluasi hubungan antara jumlah sel CD4-limfosit CD4 dan pneumonia pada anak terinfeksi HIV. **Metode :**

Penelitian *cross-sectional* dilakukan pada semua anak yang didiagnosis dengan dan tanpa pneumonia yang mengidap HIV di Rumah Sakit Adam Malik, Medan. Data diambil dari catatan medis pasien antara Januari 2008 sampai Desember 2015. Peneliti meneliti demografis, klinis, radiologis dan jumlah sel T-limfosit CD4 pada saat masuk, serta hasil *outcome* mortalitas. **Hasil :** Sebanyak 174 anak terinfeksi HIV disertakan dalam penelitian ini. Pneumonia ditemukan pada 47 anak dengan 39 bulan sebagai median usia onset. Perbedaan rata-rata pada tingkat CD4 adalah 0,912 unit (95% CI sampai -5,79 sampai 7,62) dengan *mean* lebih tinggi pada kelompok pneumonia dibandingkan kelompok non-pneumonia, namun tidak ada perbedaan yang signifikan. Selain itu, tidak ada hubungan yang signifikan antara status gizi dan kejadian pneumonia [OR 1.050; 95% CI 0,537 sampai 2,053); P = 0,886) atau antara status imunodefisiensi dan pneumonia, [OR 0,986; (95% CI 0,25 sampai 3,885); P = 0,984]. Infeksi oportunistik yang umum pada subyek yang diteliti selain pneumonia adalah diare, kandidiasis oral dan TB paru, atau kombinasi antara keduanya. Malnutrisi berat juga terjadi pada beberapa subjek. **Kesimpulan :** Tidak ada hubungan yang signifikan antara jumlah sel T CD4 + dan pneumonia pada anak terinfeksi HIV.

Kata kunci **:** *CD4, HIV, pneumonia, anak-anak*
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INTRODUCTION

The epidemic of HIV infection has made it a major worldwide health problem (UNAIDS, 2013).As the number of HIV/AIDS cases in adults has increased in Indonesia, Indonesian children also have a higher risk for infection (Phanuphak et al, 2015; Penazzato et al, 2015). Several conditions lead health workers to suspect HIV infection in children, such as the presence of recurrent infection or uncommon infection that does not heal with regular treatment, as well as accompaniment of malnutrition and failure to thrive. In fact, often the signs and symptoms of opportunistic infections are the first presentation of clinical symptoms of HIV (UNAIDS, 2013; Martens dan Lewin, 2014).

The main characteristic of HIV infection is a decline of the immune system function resulting in a great variety of opportunistic infections, malignancies, and impaired function of various organs, either directly or indirectly (Deeks, Lewin, dan Havlir, 2013).Respiratory disease is the largest cause of morbidity and mortality in HIV. Respiratory infection is one of the opportunistic infections that often affects children with HIV, mostly in the form of pneumonia in children (55%) or adults, usually occurring when CD4 counts are less than 200 cells/ mm^3(Neuman et al, 2011; Morrow et al, 2014).

METHODS

A cross-sectional study was conducted to assess for an association between CD4 T-lymphocyte cell counts and pneumonia in HIV-infected children. We included all HIV-positive children diagnosed with or without pneumonia at Adam Malik Hospital, Medan. Data were taken from patient medical records dated January 2008 to December 2015.

We studied demographic, clinical, and radiological data, as well as CD4 T-lymphocyte cell count on admission, and mortality outcomes.

Inclusion criteria were patients infected with HIV who received treatment at H.Adam Malik Hospital, below the age of 18 years, who met the criteria for HIV diagnosis in the study period of 2008-2015, and were clinically and radiologically proven infected pneumonia from 2008 to 2015. Patients without CD4 test results were excluded.

The data were entered, processed and analyzed using SPSS for Windows version 21.0 software. We used Chi-square test to assess for an association between CD4+ T-lymphocyte cell counts and pneumonia. Independent T-test was used to assess for relationships among variables. Results were considered to be statistically significant for $P < 0.05$, with 95% confidence intervals.

RESULTS

The baseline characteristics of subject can be seen in Table 1.

Mann-Whitney test revealed that mean CD4+ levels in the pneumonia and non-pneumonia groups were not significantly different (P=0.777) (Table 2).

Table 3 shows that Chi-square test revealed no significant association between immunodeficiency status of HIV-infected children and pneumonia [OR=0.986; (95%CI 0.25 to 3.885); P=0.984].

Table 1. Baseline characteristics of subjects

	Pneumonia (n=47)	No pneumonia (n=127)	P value
Mean age (SD), years	39.79 (35.23)	43.95 (35.74)	0.494
Sex, n			
Male	33	69	0.059
Female	14	58	
Nutritional status, n			
Mild malnutrition	22	61	0.886
Severe malnutrition	25	66	
Immunodeficiency status,n			
No	3	8	0.984
Yes	44	119	

Table 2. Mean difference in CD4+ levels in HIV-infected children with and without pneumonia

	(N=174)	Mean SD count (SD)	Mean difference in CD4+ levels (95%CI)	P value
Pneumonia, n	47	18.72 (4.59)	0.912 (-5.79 to 7.62)	0.777
No pneumonia, n	127	17.81 (1.18)		

Table 3. Association between immunodeficiency status in HIV-infected children with and without pneumonia

Immunodeficiency status	Pneumonia n=47	No pneumonia n=147	P value	OR (95% CI)
Yes, n(%)	44 (93.6)	119 (93.7)	0.984	0.986 (0.25 to 3.885)
No, n(%)	3 (6.4)	8 (6.3)		

Table 4. Association between nutritional status of HIV-infected children and pneumonia

Nutritional status	Pneumonia n=47	No pneumonia n=147	P value	OR (95% CI)
Severe malnutrition, n(%)	25 (53,1)	66 (44,8)	0.886	1.050 (0.537 to 2.053)
Mild malnutrition, n(%)	22 (46,8)	61 (41,4)		

Table 5. Opportunistic infections in HIV-infected children, besides pneumonia

Opportunistic infections	% of total (N=174)
Diarrhea	11
Oral candidiasis	56
Pulmonary TB	30
Varicella	1
CMV	1
Herpes simplex	1

CMV: cytomegalovirus

As shown in Table 4, Chi-square test revealed no significant association between nutritional status and pneumonia in HIV-infected children [OR= 1,050; (95%CI 0,537 to 2,053); P=0.886].

Opportunistic infections other than pneumonia that we observed in our subjects were diarrhea (11%), oral candidiasis (56%), pulmonary TB (30%), varicella (1%), CMV (1%), and herpes simplex (1%) (Table 5).

DISCUSSION

The AIDS epidemic is the biggest challenge facing the current generation, especially with regards to childhood infection, which is growing at a fast rate. Before the availability of optimal antiretroviral combination therapy regimens, infant AIDS patients survived only to the age of 12 to 18 months after an AIDS diagnosis. Opportunistic infection is the main cause of death in HIV-infected children (Fairlie et al, 2015; Davies et al, 2015). In an Indian study, the prevalence of opportunistic infections was 26% in children infected with HIV (Sanjeeva et al, 2016). A similar prevalence rate was observed in a US study, where out of 339 patients, 76 had opportunistic infections, giving an overall prevalence of 22.4% (Yadav, Nanda, dan Sharma, 2014). In addition, the Indian study reported that in 58 HIV-infected children, manifestations were canker sores (43%), tuberculosis (TB) (43%), hepatosplenomegaly (14%), lymphadenopathy (14%), papulopruritic dermatitis (10%), and chronic diarrhea (7%) (Sanjeeva et al, 2016). Similarly, the predominant opportunistic infections in other studies in children with HIV included serious bacterial infections such as pneumonia, tuberculosis, non-tuberculosis mycobacterial infection (Yadav, Nanda, dan Sharma, 2014; Balkhair et al, 2012). TB is the most frequent opportunistic infection in children in India (Sanjeeva et al, 2016).Other studies have concluded that *Pneumocystis jiroveci* pneumonia is the most frequent opportunistic infection among their study population, followed by cryptococcal meningitis, CMV retinitis, extra-pulmonary tuberculosis, and cerebral toxoplasmosis (Balkhair et al, 2012). The prevalence of pneumocystis pneumonia (PCP) was reported to be 79,8%.Theodorratou *et al*.

reported that the prevalence of PCP and bacterial pneumonia was 3.8%. Differences in the prevalence rates in the study may have been related to differences in sample size, geographic location, and demographic profiles (Theodoratou*et al*, 2010).

Opportunistic infections experienced by our HIV-infected subjects other than pneumonia were diarrhea (11%), oral candidiasis (56%), pulmonary TB (30%), varicella (1%), CMV infection (1%), and herpes simplex infection (1%).

In Nigeria, 63.6% of 173 children with HIV were malnourished. Among the malnourished children, 52.0% had severe immunosuppression status compared to children with normal weight (31.3%) (Brown*et al*, 2011). Malnutrition is associated with an increased risk of severe immunosuppression. HIV infection accompanied by malnutrition is indicative of the degree of disease severity (Munthali*et al*, 2015).This observation was consistent with West Africa research which showed that marasmus was the most common form of malnutrition associated with HIV (Bwakura-Dangarembizi*et al*, 2014). Research in Africa reported a weight loss and failure to thrive in 35.6% of 317 children with HIV infection (Zanoni*et al*, 2011). The majority of these children were in the 11 to 15 years age group, followed by the 6 to 10 years age group. Only 11 cases were under the age of 6 years. Distribution of sexes were 52% male and 48% female (Sanjeeva et al, 2016). A similar study done by Morrow*et al*. (2014) in South Africa showed that of 109 HIV-infected children with pneumonia, 47% were male and 62% were female. In our study, 174 children with HIV at Adam Malik Hospital from 2008 to 2015 had a mean age of 39 months and the mean of age was 35.23. We also found that 33 males and 14 females had pneumonia compared to 69 males and 58 females without pneumonia.

A Swiss study concluded that at the onset of HIV in children, 30% had a CD4 count <200 cells/mm^3 and 40% had a CD4 percentage <20%. The risk of opportunistic infections increased 2.5 times at a CD4 cell count of 51-200 cells/mm^3. This risk increased to 5.8 times for <50 cells/mm^3 compared to children with higher levels of CD4+> 200 cells/mm^3(Collins*et al*, 2010). Various studies have shown that lower CD4 cell counts were associated with an increased prevalence of opportunistic infection. Disease severity and frequency of opportunistic infections increases when CD4+ levels are below 200 cells /mm^3. The average levels of CD4+ cells in HIV-infected patients at the time of initial diagnosis was 333 cells/mm^3 (9.2%), while for patients with oral candidiasis the average level was 541 cells/mm^3 (17.46%).[9]Research in South Africa found that the mean CD4+ levels in HIV-infected children with pneumonia was 17,1 cells/mm^3 compared to 21 cells/mm^3 children who did not have pneumonia (Davies, 2015).There are a wide range of CD4 cell counts and percentages of different early, opportunistic infections when first infected HIV (Collins*et al*, 2010; Gingi dan Morris, 2013). In our study, mean CD4+ levels in HIV-infected children with pneumonia was 18.72 cells/mm^3 compared to 17.81 cells/mm^3 children who did not have pneumonia. But this difference was not significantly different.

In conclusion, that there is no significant association between CD4 T-lymphocyte cell counts and pneumonia in HIV-infected children.

CONFLICT OF INTEREST

None declared.

REFERENCES

Global HIV/AIDS response, (2013), *Epidemic update and health sector progress towards universal access-progress report 2013*. United Nations Progamme on HIV/AIDS. [Cited 2016 March]. Available from: http://www.unaids.org/sites/default/files/media_asset/20111130_UA_Report_en_1.pdf

Phanuphak, N., Lo, YR., Shao, Y., Solomon, SS., Connell, RJO., *et al*., (2015), HIV Epidemic in Asia: Implications for HIV vaccine and other prevention trials, *AIDS research and human retrovirus*, 31, pp.1-17

Penazzato, M., Revill, P., Prendergast, AJ., Collins, IJ., Walker, S., Elyanu, PJ., *et al*., (2014), Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all?. *Lancet Infect Dis*., vol.14(7), pp.650-5, doi: 10.1016/ S1473-3099(13)70262-7, Epub 2014 Jan 21.

Maartens, G., Celum, C., Lewin, SR., (2014), HIV infection: epidemiology, pathogenesis, treatment, and prevention, *Lancet*. Vol.384, pp.258–71.

Deeks, SG., Lewin, SR., Havlir, DV., (2013), The end of AIDS: HIV infection as a chronic disease, *Lancet*, vol.382, pp.1525–33

Neuman, MI., Monuteaux, MC., Scully, KJ., Bachur, RG., (2011), Prediction of pneumonia in a pediatric emergency department. *Pediatrics J*. vol.128, pp.246-53.

Morrow, BM., Samuel, CM., Zampoli, M., Whitelaw, A., Zar, HJ., (2014), Pneumocystis pneumonia in South African children diagnosed by molecular methods. *BMC Research Notes*. Vol.7(26), pp.1-6

Fairlie, L., Karalius, B., Patel, K., van Dyke, RB., Hazra, R., Hernán, MA., *et al*., (2015), CD4+ and viral load outcomes of antiretroviral therapy switch strategies after virologic failure of combination antiretroviral therapy in perinatally HIV-infected youth in the United States. *AIDS*. vol.29, pp.2109-19.

Davies, MA., Ford, N., Rabie, H., Fatti, G., Stinson, K., Giddy, J., *et al*., (2015), Reducing CD4 monitoring in children on antiretroviral therapy with virologic suppression, *Pediatr Infect Dis J*. vol.34, pp.1361-4.

Yin, DE., Warshaw, MG., Miller, WC., Castro, H., Fiscus, SA., Harper, LM., *et al*., (2014), Using CD4 percentage and age to optimize pediatric antiretroviral therapy initiation, *Pediatrics*, vol. 134, pp.1104-16.

Sanjeeva, GN., Gujjal, CP., Pavithra, HB., Sahana, M., Sunil, K DR., Hande, L., (2016), Predictors of mortality and mortality rate in a cohort of children living with HIV from India, *Indian J Pediatr*, vol.83, pp.765-71.

Yadav J, Nanda S, Sharma D. (2014). Opportunistic infections and complications in human immunodeficiency virus-1-infected children: correlation with immune status. Sultan Qaboos Univ Med J. 2014:14:513-21.

Balkhair, AA., Al-Muharrmi, ZK., Ganguly, S., Al-Jabri, AA., (2012), Spectrum of AIDS defining opportunistic infections in a series of 77 hospitalised HIV-

infected Omani patients. *Sultan Qaboos Univ Med J*. vol.12, pp.442–8.

Theodoratou, E., Al-Jilaihawi, S., Woodward, F., Ferguson, J., Jhass, A., Balliet, M., Kolcic, I., *et al.*, (2010), The effect of case management on childhood pneumonia mortality in developing countries, *Int J Epidemiol*. Vol.39, pp.155-71.

Brown, BJ., Oladokun, RE., Odaibo, GN., Olaleye, DO., Osinusi, K., Kanki, P., (2011), Clinical and immunological profile of pediatric HIV infection in Ibadan, *Nigeria. J Int. Assoc. Physicians AIDS Care*. Vol.10, pp.49-53

Munthali, T., Jacobs, C., Sitali, L., Dambe, R., Michelo, C., (2015), *Mortality and morbidity patterns in under-five children with severe acute malnutrition (SAM) in Zambia: a five-year retrospective review of hospital-based records (2009–2013)*, Archives of Public Health, vol.73(23), pp.1-9

Bwakura-Dangarembizi, M., Kendall, L., Bakeera-Kitaka, S., Nahirya-Ntege, P., Keishanyu R, Nathoo K, *et al.* (2014), A randomized trial of prolonged cotrimoxazole in HIV-infected children in Africa, *N Engl J Med*, vol.370, pp.41-53.

Zanoni, BC., Phungula, T., Zanoni, HM., France, H., Feeney, ME., (2011), Risk factors associated with increased mortality among HIV infected children initiating antiretroviral therapy (ART) in South Africa, *PloS ONE*, vol.6, pp.1-6.

Collins, IJ., Jourdain, G., Hansudewechakul, R., Kanjanavanit, S., Hongsiriwon, S., Ngampiyasakul, C., *et al.*, (2010), Long-term survival of HIV-infected children receiving antiretroviral therapy in Thailand: a 5-year observational cohort study, *Clin Inf Dis.* Vol.51, pp.1449-57.

Gingo, MR., Morris, A., (2013), Pathogenesis of HIV and the lung, *Curr. HIV/AIDS Rep*. vol.10, pp.42–50.