

Characteristics of Anemia in Children with HIV Infection

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Abstract

Anemia is a hematologic complication commonly encountered in HIV patients. Although the severity of anemia is generally mild, anemia has been shown to be a strong risk factor for disease progression, particularly in HIV infected person. With different severity and types of anemia in HIV patients, it is necessary to identify the severity and type of anemia in HIV-infected children, thus helping to determine the prognosis and management of their anemia. The purpose of this study was to describe HIV patient staging infection, co-morbidities, and type of anemia in HIV-infected children based on their therapy. A descriptive quantitative research was conducted in Dr. Hasan Sadikin General Hospital Bandung. Data were collected from patients' medical records diagnosed with HIV between 2015–2017. The severity of anemia was set according to World Health Organization standards in 2011 and the types of anemia were identified from the erythrocyte index on routine hematologic examination. Forty-seven of 73 children had anemia. Based on the severity of anemia, 26% mild anemia, 60% moderate anemia, and 15% severe anemia were found. Subsequently, hypochromic microcytic (40%), macrocytic (32%), and normocytic normochromic (28%) anemia were identified. Considering the direct and indirect mechanism to yield anemia in HIV-infected patients, this double sword symptom becomes the most common complication burdened the growth and development of HIV-infected children. This study made it even more pronounced.

Key words: Anemia, Children, HIV

Karakteristik Anemia pada Anak Terinfeksi HIV

Abstrak

Anemia adalah komplikasi hematologi paling sering ditemukan pada pasien HIV. Meskipun tingkat anemia pada umumnya ringan, anemia telah terbukti menjadi faktor risiko kuat terhadap perkembangan penyakit. Terdapat perbedaan tipe anemia pada pasien HIV dengan etiologi yang berbeda pula sehingga perlu dilakukan identifikasi mengenai tingkat dan tipe anemia pada pasien HIV anak, yang pada akhirnya dapat membantu menentukan prognosis dan penatalaksanaan anemia pada pasien ini. Suatu penelitian deskriptif kuantitatif ini bertujuan mengetahu tingkat dan tipe anemia dengan mengklasifikasikannya berdasarkan komorbiditas pada pasien HIV/AIDS anak di RSHS tahun 2015–2017 menggunakan data rekam medik pasien pemeriksaan hematologi rutin. Tingkat anemia ditetapkan berdasar atas standar WHO, sementara jenis anemia dilihat dari indeks eritrosit. Sebanyak 73 pasien anak terinfeksi HIV, didapatkan 47 anak mengalami anemia. Tingkat anemia ditemukan anemia ringan (26%), anemia sedang (60%), dan anemia berat (15%). Tipe anemia yang ditemukan adalah normositik normokromik (28%), makrositik (32%), dan mikrositik hipokromik (40%). Tingkat anemia pada pasien HIV anak di RSHS pada umumnya adalah anemia sedang. Tipe anemia terbanyak pada penelitian adalah mikrositik hipokromik.

Kata kunci: Anak, anemia, HIV

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Introduction

Anemia is the most common hematologic complication in HIV-infected patients with an incidence rate ranging from 1.3% to 95%.^{1,2} The number of new HIV cases in Indonesia from year to year tends to increase and in 2016 it was reported as many as 41,250 cases with 3.2% of them occurring in children.³

There are many advances in HIV infection management that can facilitate faster diagnosis and improve treatment outcomes, but the complications remain high. Many factors that contribute to the incidence of anemia in HIV patients included nutritional deficiencies such as iron or vitamin B12, opportunistic infections, malignancy, drug therapy, and the direct effects of the HIV virus.⁴⁻⁷ Previous studies suggested that anemia is a strong risk factor for disease progression and increase the risk of death if left untreated.^{1,2,6}

The previous study had been done in different countries revealed various anemia results depend on their geography, ranging from mild to severe symptom.⁸ However, the knowledge of the characteristic of anemia in HIV children patients has not been widely discussed, particularly in a country with high prevalence of HIV infection, such as Indonesia. The aim of this study was to determine the severity and type of anemia in HIV-infected children, thus providing data to determine the prognosis and provide information for clinical management in HIV-infected children.

Methods

A descriptive quantitative study was done analyzing hematological data taken from the medical records of patients diagnosed with HIV at the Teratai Clinic of Dr. Hasan Sadikin General Hospital, Bandung. This study included children (<18 years) who had been diagnosed with HIV either receiving ARV drugs, performed hematological checks (hemoglobin and erythrocyte index), from January 2015–June 2017. Patients receiving anemia supplementation and having incomplete medical record data were excluded. This study has been approved by the Ethics Committee of Faculty of Medicine, Universitas Padjadjaran with ethical clearance No. 394/UN6.C.10/PN/2017.

We recorded hematological data using result of Sysmex XT 2000i automatic hemato-analyzer (Sysmex Corp., Tokyo, Japan). We divided the

severity of anemia based on hemoglobin level according to World Health Organization into severe, moderate, and mild.⁹ The type of anemia was characterized by erythrocyte index which is the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) classified into microcytic hypochromic, normocytic normochromic and macrocytic.⁴ Data descriptively analyzed using Microsoft Excel 2010 Windows Version 14.0.4734.1000.

Results

Seventy-three data from HIV-infected children was obtained. Of all, 47 patients (64%) had anemia. The demographic characteristics of HIV children patients was listed in Table 1. The age of HIV-infected children affected by anemia in this study had a median of 5.2 years old (interquartile range: 2.7–7.3). Of 47 patients with HIV anemia, 76% of patients had reached stage 4

Table 1 Characteristics of HIV Children Patients

	(n=47)	%
Sex		
Female	24	51
Male	23	49
Age (years old)		
0,5–4	22	47
5–10	20	42
11–18	5	11
HIV		
Stage 1	3	6
Stage 2	1	2
Stage 3	7	15
Stage 4	36	77
Comorbidities		
Infections		
Pulmonary	17	36
Tuberculosis		
Pneumonia	10	21
Oral candidiasis	7	15
Etc.	5	11
Non-infection		
Malnutrition	19	40
Cerebral palsy	2	4
Cardiomyopathy	2	4
Etc.	10	21

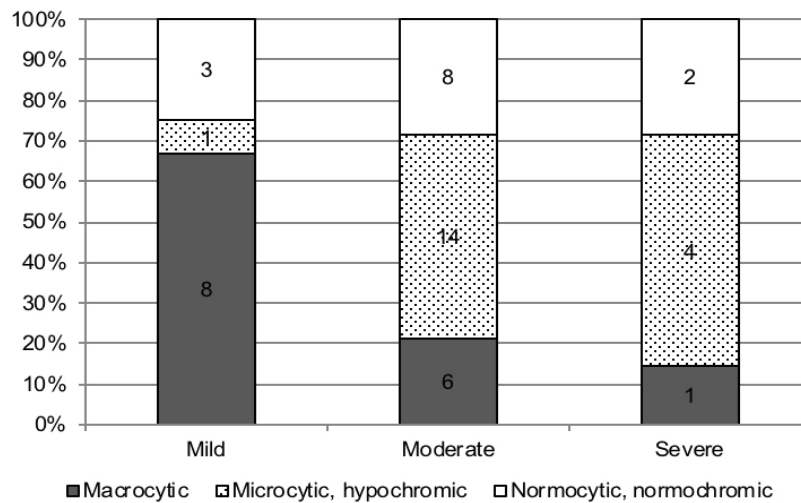


Figure Type of Anemia

HIV. Comorbidities experienced by 37 patients with the most common infectious disease was pulmonary TB with 61% of patients and the most common non-infectious disease was malnutrition with 40% of patients. In addition

to receiving anti-retroviral drugs, HIV patients also received anti-tuberculosis, antibiotics, antifungal, etc., which are shown in Table 2. The most frequently administered retroviral drugs were lamivudine (66%) and zidovudine (63.8%).

Hematology profile with a reference value from WHO⁹ and Greer et al.,⁴ was shown in Table 3. The median hemoglobin was of 9.6 g/dL (interquartile range: 8.2-10.6), with most of the patients included in moderate anemia. The average MCV value of this study was 83.9±10.7 fl, MCH 27.4±4.2 pg, and MCHC 32.9±1.8%. Figure shows the distribution of severity of anemia based on WHO⁹ based on erythrocyte morphology (hypochromic microcytic, normocytic normochromic, and macrocytic).⁴

Table 2 Pharmacological Therapy Used

	(n=47)	%
Antiretroviral		
Lamivudine	31	66
Zidovudine	30	64
Nevirapine	25	53
Efavirenz	7	15
Abacavir	2	4
Tenofovir	1	2
Anti-tuberculosis		
Ethambutol	12	25
Rifampicin	11	23
Isoniazid	9	19
Pyrazinamide	6	13
Antibiotics		
Cotrimoxazol	31	66
Gentamicin	10	21
Ampicillin	8	17
Metronidazole	6	13
Others	19	40
Antifungal	12	25,5
Others	26	55,3

Table 3 Hematological Profile

Parameter	Patients Value
Hemoglobin, g/dL (Median, (IQR))	9,6 (8,2-10,6)
MCV, fl (Mean±SD)	83,9±10,7
MCH, pg (Mean±SD)	27,4±4,2
MCHC, % (Mean±SD)	32,9±1,8
Erythrocyte, millions/μL (Mean±SD)	3,4±0,6

Discussion

Anemia has been known to be a clinical problem in HIV patients, suggesting a possible physiological change in regulation of red blood cell formation caused by virus infection¹. Pulmonary tuberculosis was the most common comorbid infectious disease found in this study. The patients in this study were currently in the middle of various treatments like antiretroviral, anti-tuberculosis, antibiotics, antifungal, and others. Lamivudine and zidovudine were frequently administered in this study. The results of erythrocyte index based on overall mean rate of anemia in HIV patients in this study was hypochromic microcytic.

The mechanism of the occurrence of anemia in HIV infection is known from the study of Redig and Berline¹ that the HIV has a direct effect through the proteins of the virus in the blood cell-forming progenitor cells and the erythropoietin (EPO) response thereby suppressing the formation of red blood cells. Protein p17 in HIV-1 virus mimicry with EPO causing auto-antibody to endogenous EPO. This study showed the anemia has emerged since a young age, although there is no data on the number of viruses infecting, it needs important attention in the management of antiviral administration.

Anemia in HIV-infected patients can also be caused and exacerbated by the side effects of antiretroviral drugs (ARVs). Anemia in HIV patients in antiretroviral treatment improves anemia caused by the HIV virus effectively in both pediatric and adult patients.¹ Nonetheless, the zidovudine regimen ARV has anemia-related side effects associated with bone marrow suppression.^{10,11} Shet et al.¹² in their study shown that of 38 non-anemic HIV-infected children, nine children were anemic 6 months later, and 3 of them were attributed to zidovudine-related bone marrow suppression. Most of HIV-infected children in this study were received zidovudine regimen.

Anemia condition certainly affect the quality of life of HIV-infected patients. Anemia can reduce survival rates, accelerate disease progression, and increase mortality in HIV-infected patients.^{1,6} According to WHO, the severity of anemia is differentiated into mild, moderate, and severe.⁹ The severity of anemia found in this study is even worse compared with studies in Ethiopia, which is state with the common severity of anemia is mild (60.5%).⁸ The different severity of anemia in this study may occur due to several factors such as opportunistic infections, nutritional

deficiencies, antiretroviral therapy, zidovudine, and the HIV virus itself.^{1,6,7}

HIV virus has the characteristic of infecting CD4 cells so that the cells gradually decrease over time.⁴ The decrease of CD4 cells will result in easy infection with other infections or opportunistic infections. In this study, we found that most the patients had a history of comorbidities with the most common infectious disease pulmonary TB and the most non-infectious disease was malnutrition. This study did not have complete CD4 cell count data, therefore it is essential to analyze the association of these cells with severity and types of anemia. Chronic inflammation increases cytokines, including IL-1, IL-6, and TNF- α -related co-morbid, including anemia. IL-6 has a significant role in the occurrence of anemia through its role in hepcidin regulation¹. Yaranal et al.¹³ study explains that out of 100 adult pulmonary TB patients, 74% of patients have anemia associated with a dull response in erythropoiesis in the bone marrow, TNF- α and other cytokines that suppress EPO production.

HIV patients can have any type of anemia and have many risk factors such as micronutrient deficiencies or specific ARV use. Anemia in the HIV population generally has the characteristics of low reticulocyte counts, normochromic and normocytic anemia, normal iron, and EPO response damage, which explains an anemia relationship with inflammation or more commonly referred to as anemia due to chronic infection.¹ In contrast to this study, the most common type of anemia is microcytic hypochromic. Johannessen's result shown the same proportion that 39.1% of patients have a type of microcytic hypochromic anemia caused by iron deficiency,¹⁰ while study in Ethiopia shows that the most common type of anemia is normocytic normochromic 46.5%.⁸ Folate and vitamin B12 were important for DNA synthesis. Low vitamin B12 and folate status has been associated with poor immunological status and HIV disease progression, while zidovudine causes inhibition of nucleoside reverse transcriptase, in both condition causing delayed DNA replication and accumulate more protein leads to a larger orthochromatic erythroblasts, form macrocytic erythrocytes.¹⁴⁻¹⁶ In this study, as shown in Figure 1, although the most common type of anemia is microcytic hypochromic, from 12 patients with mild anemia mostly had macrocytic anemia, this may be due to patients receiving zidovudine therapy, and only 1 patient had comorbid.

According to Shaw and Friedman¹⁷ in the inflammatory response, IL-6, hepcidin is

synthesized. Heparin causes sequestration of bio-available iron form into storage form and reduces intestinal absorption of iron. Both processes are caused by the binding of hepcidin to ferroportin. The hepcidin-ferroportin bond causes internalization and degradation of ferroportin, thus trapping iron in cells. The reduction of absorption and sequestration of iron, leading to reduced iron bioavailability to achieve needs such as erythropoiesis. In this study found 60% of patients had chronic infections and 40% had malnutrition, which increases the possibility of anemia due to iron deficiency and gave a microcytic hypochromic description.

Limitation of this study that no data regarding cellular and molecular of patients' inflammatory profile such as CD4 count, IL-1, IL-6, and TNF- α -related co-morbid. Therefore, further study need to be done in building the profile inflammatory cytokine in HIV-infected children.

In conclusion, considering the direct and indirect mechanism to yield anemia in HIV-infected patients, this double sword symptom becomes the most common complication burdened the patient since their child development. This study made it even more pronounced. The most common type of anemia found in HIV-infected children is hypochromic microcytic. Therefore, it is important to make early diagnosis and provide appropriate treatment in order to reduce the risk of anemia in HIV patients, especially children.

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