EFFECT OF ANTI-TUBERCULOSIS MULTI DRUG RESISTANCE REGIMEN ON HEMATOLOGICAL LUNG TUBERCULOSIS PATIENTS PROFILE WITH MULTI DRUG RESISTANCE

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Abstract: ATD administration of tuberculosis in combination and duration often causes multi drug resistance (MDR) ATD due to discontinuation of treatment. Reported hematologic abnormal changes due to ATD. This study investigated hematological changes before and during MDR therapy of MDR TB patients in Tuberculosis MDR RSUD Ulin Banjarmasin from September to December 2017. The study population was patients treated in TB MDR Poly and selected samples with a time-limiting method. Inclusion and exclusion criteria were MDR-TB patients detected by Gene Xpert® examination, treated <30 days, between 18 and 65 years of age, HIV negative, as well as identification and laboratory data recorded in the complete medical record. 17 samples collected by hematological parameters were collected. There were significant changes in hemoglobin, hematocrit, platelets, RDW-CV, MCV, eosinophils, lymphocytes, granulocytes, and monocytes after treatment. It was concluded that MDR regimen ATD did not cause anemia and thrombocytopenia. There was also no significant change in WBC even though the count of the species changed significantly

Keywords: Tubeculosis, Multi Drug Resistency (MDR), Anti Tuberculosis Drugs (ATD), profil hematologis

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis which can infect various organs and tissues of the human body, especially the lungs. The easy spread by the inhalation of bacteria through the respiratory tract leads to high virulence and pathogenicity of TB, making it a major health problem in the world in preventing and treating it.[1]

It is estimated that one third of the world's population is infected with M. tuberculosis and at risk of active TB. The largest number of TB cases are found in the African and Asian continents, particularly in India and China, which account for 40% of all cases of TB cases worldwide. In Indonesia alone up to 2014 is 322,806 cases with 22,000 cases of which are TB cases with resistance to treatment therapy.[1,2]

TB treatment is done with antibiotics capable of killing M. tuberculosis. A group of antibiotics that can cure TB is known as an anti-tuberculosis drug (ATD). ATD is administered in combination and over a long period of time in TB treatment programs so that it often leads to treatment side-effects that cause the treatment program to break down. This led to the emergence of new problems of resistance to ATD.[3]

Side effects that appear on the use of ATD can be allergic reactions, fever, skin disorders, vasculitis, nausea, vomiting, hepatotoxicity, hepatocellular inflammation, peripheral neuropathy, and others. For that, we need complete assessment of the condition of TB patients before undergoing ATD therapy such as laboratory examination (hematology and blood chemistry), heart record, audiometric status, psychological status, nutritional status and so forth.[3,4]

There have been reported abnormal changes in hematologic value due to ATD administration in TB patients. Rifampicin and isoniazid were investigated in Japan by Nagayama et al in 2004 causing leucopenia in 2.3% of its users, while Malaysian Muzafar et al in 2008 reported that 88.2% of ATD users in TB spondylitis patients had normochromic anemia. Leukocytosis in 36 patients and thrombocytosis in 24 patients was also reported based on the results of Yaranal et al's study in India in 2013, in contrast to results published by Maartens et al. From a 1990 South African study showing 14% leucopenia, thrombocytopenia 23%, and lymphopenia by 87%. Recent studies reported by Kassa et al in Ethiopia in 2016 show the results of hemodilution caused by anemia and thrombocytopenia of 38.5% of all study subjects.[5-9]

Hematologic profile changes are expected to be more diverse in cases of TB with ATD resistance, including resistance to the most potent ATD classes of Isoniazid (H) and Rifampicin (R). Treatment given to multi-drug resistance conditions (Multi Drug Resistance - MDR) is a combination of sensitive ATD in larger types and longer delivery periods. However, there have been no reported studies examining the hematologic profile changes in patients with MDR TB who received ATD regimens besides I and R and in the long term. Hence, a study will be conducted on the changes of hematologic profile in patients with MDR TB before and during MDR therapy regimen.[10]

RESEARCH METHODS

The study was a longitudinal retrospective observational analytic study of patients with MDR TB undergoing therapy with MDR regimens at MDR Regional Ultrasound Hospital (RSUD) Ulin Banjarmasin in September to December 2017 by comparing the results of hematologic laboratory tests before and during undergoing MDR TB treatment.

The study population came from patients who were treated at TB MDR Clinic Ulin Banjarmasin Hospital to get the MDR regimen treatment dutifully. Samples were

selected by time restriction method. All patients who visited MDR TB clinic to undergo therapy were recruited to follow the study with inclusion and exclusion criteria of MDR TB patients were detected through a Molecular Rapid Assay in the form of Gene Xpert®, had undergone MDR therapy for at least 30 days, aged over 18 years and under 65 years old, not infected with HIV, as well as the identity of medically recorded data and laboratory results in the medical record. Patients newly diagnosed and who have not received MDR regimen therapy or who have completed a treatment program are not included in the study. Using the inclusion and exclusion criteria of the patients, 17 patients were included in the study.

Socio-demographic data such as age and sex were collected from the patient's medical records. The age group was divided according to the growth stage stature of young adults (18 to 40 years), adults (41 to 65 years) and the elderly (> 65 years).[11]

The haematological parameters collected were hemoglobin, erythrocyte, hematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), leukocyte count, leukocyte count, number of platelets, and count leukocyte types (granulocytes, lymphocytes, and MID). The parameters were taken from a blood test in the clinical pathology laboratory of Ulin Hospital with Mindray® hematology machine before undergoing therapy and during therapy. These data were secondary data obtained from the patient's medical records.

Data was checked, sorted, categorized and coded manually and then transferred to SPSS version 20 for analysis. Frequency and cross tabulation were used to present descriptive statistical data. A paired T-test was used in the analysis to compare hematologic values before and during patients undergoing MDR therapy if the distribution of data was normal and homogeneous. P values less than 5% were considered statistically significant.

Ethical approval was obtained from research ethics committee of Medical Faculty of Lambung Mangkurat. Research permit and application of medical record data was also submitted to Director of Ulin General Hospital Banjarmasin through Research and Development Division.

RESULTS AND DISCUSSION

A total of 17 patients with MDR pulmonary tuberculosis from 40 patients who were treated at Tuberculosis MDR Clinic in Ulin General Hospital period September to December 2017 and meet the inclusion and exclusion criteria involved in this study. From the study sample, the largest socio-demographic group was male (70% versus 30%), with the largest age group being the age group between 45-59 years (47%), then age group under 45 years (35%), and the smallest group is the age group above 60 years. The mean age in this study was 47.06 ± 12.67 years with a range from the age of 21-75 years.

Patients involved then performed laboratory tests to look at their hematological profile, before starting anti tuberculosis drug therapy MDR regimen and as long as they took the drug. The hematologic profile examined was hemoglobin (Hb), leukocyte (erythrocyte), hematocrit (Hct / hematocrit), platelet (platelet), red cell distribution (RDW-CV red blood cell distribution width), mean red corpuscular volume (MCV), mean hemoglobin of MCH / mean corpuscular hemoglobin, mean concentrations of MCHC / mean corpuscular hemoglobin concentration, and count leukocyte type (Bas / basofil, Eus / eosinophil, Gra / granulocyte, Lim / lymphocytes and Mon / monocytes).

The examination results of these parameters are then analyzed statistically and presented in table 1.

Tabel 1. Haematological parameters changes in MDR TB patients before and after therapy using ATD of MDR regimen

Parameters	Before Therapy	After Therapy	P-value
Hb (g/dL)	11.89±1.77	13.29±1.80	0.001*
WBC ($x10^3$/uL)	9.34±2.92	8.28±2.67	0.122
RBC ($x10^6$/uL)	4.61±0.71	4.87±0.56	0.241
HCT (vol%)	36.61±0.56	40.71±4.63	0.019*
PLT ($x10^3$/uL)	366.24±141.21	295.47±108.09	0.002*
RDW-CV (%)	14.7±2.24	13.43±1.63	0.038*
MCV (fL)	80.03±8.40	83.97±7.67	0.010*
MCH (pg)	26.21±4.39	27.61±4.89	0.434
MCHC (%)	32.59±3.108	32.74±3.78	0.794
Bas% (%)	0.42±0.27	0.41±0.30	0.727
Bas# ($x10^3$/uL)	0.0376±0.03	0.0359±0.03	0.750
Eus% (%)	4.12±4.77	8.58±10.15	0.039*
Eus# ($x10^3$/uL)	0.35±0.36	0.80±1.18	0.072
Gra% (%)	64.91±14.51	58.55±10.62	0.121
Gra# ($x10^3$/uL)	6.49±2.85	4.90±2.16	0.011*
Lim% (%)	19.80±7.80	25.25±9.05	0.030*
Lim# ($x10^3$/uL)	1.75±0.61	1.96±0.62	0.038*
Mon% (%)	7.82±1.78	7.58±3.22	0.707
Mon# ($x10^3$/uL)	0.79±0.41	0.59±0.23	0.001*

Table 1 shows that there are significant changes in hemoglobin, hematocrit, platelets, red cell distribution, corpuscular volume, eosinophil and lymphocyte count, and granulocyte, lymphocyte, and monocyte count after receiving antituberculosis drug treatment of MDR regimen.

Results of sociodemographic studies of these patients are also shown in Table 2:

Tabel 2. Hematologic parameters showing significant changes by sex and age in MDR TB patients before starting therapy compared to during MDR regimen ATD therapy

			Before Therapy	After Therapy	P-value
Hb (g/dL)	Sex	Men (70%)	12.31±1.69	13.87±1.66	0.01*
		Women (30%)	10.90±1.69	11.88±1.34	0.11
	Age (47,06±12,67)	<45 (35%)	11.58±1.56	13.08±1.94	0.1
		45-60 (47%)	11.95±2.06	13.28±1.96	0.01*
		>60 (18%)	12.36±1.85	13.70±1.58	0.07
WBC (x103/uL)	Sex	Men (70%)	8.96±2.63	7.10±1.79	0.01*
		Women (30%)	10.24±3.69	11.12±2.33	0.57
	Sex	<45 (35%)	9.16±1.28	8.84±2.69	0.83

			Before Therapy	After Therapy	P-value
	(47,06±12,67)	45-60 (47%)	10.54±3.44	9.06±2.38	0.13
		>60 (18%)	6.43±1.98	5.06±0.32	0.31
	Sex	Men (70%)	4.46±0.75	4.81±0.63	0.23
		Women (30%)	4.95±0.53	5.01±0.38	0.87
RBC (x106/uL)	Age	<45 (35%)	4.95±0.82	5.05±0.63	0.85
	(47,06±12,67)	45-60 (47%)	4.49±0.57	4.99±0.37	0.05*
		>60 (18%)	4.20±0.73	4.17±0.39	0.96
	Sex	Men (70%)	325.17±121.93	250.75±72.06	0.01*
		Women (30%)	464.80±147.40	402.80±109.77	0.15
PLT (x103/uL)	Age	<45 (35%)	459.5±111.51	362±99.65	0.03*
	(47,06±12,67)	45-60 (47%)	329.87±145.54	282.12±95.96	0.14
		>60 (18%)	276.66±104.24	198±90.35	0.20
	Sex	Men (70%)	36.76±5.62	41.51±5.08	0.05*
		Women (30%)	36.24±4.89	38.78±2.86	0.23
HCT (vol%)	Age	<45 (35%)	37.48±6.06	41.71±4.62	0.19
	(47,06±12,67)	45-60 (47%)	35.68±4.37	40.96±4.98	0.03*
		>60 (18%)	37.30±7.51	38±4.05	0.92
	Sex	Men (70%)	14.53±2.17	12.85±1.04	0.01*
		Women (30%)	15.10±2.60	14.80±2.08	0.81
RDW-CV (%)	Age	<45 (35%)	15.18±1.78	14.5±2.02	0.47
	(47,06±12,67)	45-60 (47%)	14.86±2.72	13.18±1.02	0.05*
		>60 (18%)	13.3±1.55	11.93±0.47	0.35
	Sex	Men (70%)	82.73±6.42	86.49±4.90	0.00*
		Women (30%)	73.54±9.72	77.92±10.21	0.33
MCV (fL)	Age	<45 (35%)	75.78±3.91	82.8±5.19	0.08
	(47,06±12,67)	45-60 (47%)	80.10±10.17	82.2±9.33	0.16
		>60 (18%)	88.33±2.56	91.03±2.61	0.13
	Sex	Men (70%)	27.90±3.60	29.14±4.44	0.94
		Women (30%)	22.13±3.47	23.92±4.17	0.29
MCH (pg)	Age	<45 (35%)	23.55±1.61	26±3.29	0.2
	(47,06±12,67)	45-60 (47%)	26.98±5.54	26.67±3.88	0.77
		>60 (18%)	29.46±0.85	33.3±7.18	0.49
	Sex	Men (70%)	33.675±3.07	33.62±3.78	0.61
		Women (30%)	30±0.82	30.6±1.99	0.41
MCHC (%)	Age	<45 (35%)	31.13±2.96	31.3±2.21	0.92
	(47,06±12,67)	45-60 (47%)	33.38±3.47	32.37±1.89	0.28
		>60 (18%)	33.4±1.73	36.56±7.81	0.62
	Sex	Men (70%)	0.35±0.26	0.34±0.29	0.71
		Women (30%)	0.60±0.38	0.58±0.48	0.89
Bas% (%)	Age	<45 (35%)	0.35±0.20	0.41±0.19	0.17
	(47,06±12,67)	45-60 (47%)	0.47±0.34	0.48±0.37	0.89
		>60 (18%)	0.43±0.15	0.2±0.09	0.10
Bas#	Sex	Men (70%)	0.03±0.02	0.41±0.03	0.19
(x103/uL)		Women (30%)	0.05±0.03	0.06±0.05	0.54

			Before Therapy	After Therapy	P-value
	Age (47,06±12,67)	<45 (35%)	0.03±0.02	0.03±0.01	0.61
		45-60 (47%)	0.05±0.03	0.045±0.04	0.89
		>60 (18%)	0.03±0.005	0.01±0.01	0.10
	Sex	Men (70%)	4.12±4.77	8.57±10.15	0.03*
		Women (30%)	5.78±7.33	13.94±15.85	0.41
Eus% (%)	Age (47,06±12,67)	<45 (35%)	2.36±1.39	14.05±13.39	0.03*
		45-60 (47%)	6.26±6.37	6.22±7.96	0.99
		>60 (18%)	1.93±0.45	3.9±3.01	0.43
	Sex	Men (70%)	0.34±0.36	0.80±1.17	0.07*
		Women (30%)	0.492±0.57	1.656±1.92	0.31
Eus# (x103/uL)	Age (47,06±12,67)	<45 (35%)	0.21±0.12	1.515±1.74	0.03*
		45-60 (47%)	0.53±0.46	0.48±0.53	0.85
		>60 (18%)	0.12±0.01	0.20±0.15	0.45
	Sex	Men (70%)	64.90±14.51	58.55±10.62	0.16
		Women (30%)	65.68±13.83	61.3±12.41	0.59
Gra% (%)	Age (47,06±12,67)	<45 (35%)	60.61±17.04	53.35±8.05	0.35
		45-60 (47%)	65.88±15.02	62.65±11.93	0.57
		>60 (18%)	70.87±7.50	58.03±9.62	0.25
	Sex	Men (70%)	6.49±2.84	4.89±2.16	0.01*
		Women (30%)	7.02±3.99	6.81±2.17	0.69
Gra# (x103/uL)	Age (47,06±12,67)	<45 (35%)	6.30±0.88	4.56±1.23	0.08
		45-60 (47%)	7.33±3.83	5.88±2.57	0.19
		>60 (18%)	4.61±1.75	2.91±0.45	0.29
	Sex	Men (70%)	19.80±7.80	25.24±9.04	0.01*
		Women (30%)	20.9±8.20	18.96±5.86	0.38
Lim% (%)	Age (47,06±12,67)	<45 (35%)	20.06±5.46	26.52±11.58	0.16
		45-60 (47%)	19.93±10.44	22.87±8.12	0.42
		>60 (18%)	18.91±5.37	29.03±6.27	0.20
	Sex	Men (70%)	1.74±0.60	1.96±0.62	0.03*
		Women (30%)	1.96±0.50	2.01±0.25	0.79
Lim# (x103/uL)	Age (47,06±12,67)	<45 (35%)	1.86±0.66	2.20±0.82	0.07
		45-60 (47%)	1.86±0.58	1.96±0.45	0.56
		>60 (18%)	1.2±0.26	1.46±0.37	0.21
	Sex	Men (70%)	7.81±1.77	7.58±3.21	0.58
		Women (30%)	7.04±1.99	5.28±1.16	0.14
Mon% (%)	Age (47,06±12,67)	<45 (35%)	8.26±1.78	6.71±4.19	0.34
		45-60 (47%)	7.46±1.96	7.76±2.75	0.70
		>60 (18%)	7.86±1.62	8.83±2.74	0.45
	Sex	Men (70%)	0.78±0.40	0.59±0.22	0.00*
		Women (30%)	0.716±0.28	0.58±0.14	0.14
Mon# (x103/uL)	Age (47,06±12,67)	<45 (35%)	0.77±0.25	0.53±0.20	0.27
		45-60 (47%)	0.90±0.52	0.68±0.24	0.05*
		>60 (18%)	0.5±0.13	0.44±0.13	0.29

From the table above, it can be seen that in the male gender, the hematologic parameter changes are hemoglobin, leukocyte, hematocrit, platelet count, red cell distribution range, mean red blood cell volume, eosinophil percentage, eosinophil count, granulocyte count, lymphocyte percentage, lymphocyte count, and monocyte count (P-value <0.05). While in the women's group there was no significant change in hematological parameters.

Based on age data, the age group that showed significant changes in hematological parameters were age group 45-60 years, ie on hemoglobin, erythrocytes, hematocrit, red cell distribution, and monocyte count. However, other age groups did not show significant differences from changes in hematologic parameters after receiving antituberculous drugs.

Tuberculosis infection causes a change in one's hematologic function. The change is caused by the immune system's resistance to the bacterium Mycobacterium tuberculosis. In addition, antituberculosis drug therapy also gives effect to blood cells.[3,12,13]

Haematological changes that can occur in people with Tuberculosis one of them is anemia. Anemia in TB patients is enforced based on blood Hb levels by taking into account the number of red blood cells and hematocrit. As with other chronic diseases, tuberculosis will lead to decreased hemoglobin with reduced iron levels in plasma and total iron binding capacity (TIBC / total iron binding capacity), as well as decreased MCV and MCH (hypochromic microcytic anemia). This is due to the emphasis on the process of erythropoiesis by inflammatory mediators. Thus the formation of hemoglobin is inhibited and iron bound as heme increases levels in the blood. In addition, tuberculosis will increase the production of cytokines such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), Interleukin-1 (IL-1) and interleukin-6 (IL-6). These cytokines come out due to an invasion of bacteria that activate T lymphocytes and macrophages. These cytokines will cause the distortion of converting iron ions into iron deposits in the reticuloendothelial system, thereby decreasing plasma concentrations in the plasma resulting in impaired hemoglobin production, a proliferation of erythroid proliferation barrier, and ultimately erythropoiesis disorders. In addition, the inflammatory process that causes increased TNF-α will result in decreased appetite and weight loss as is commonly complained by tuberculosis patients. Granuloma formation can also occur due to infection of M.Tb bacteria in the bone marrow so that the process of formation of red blood cells is inhibited. Nutritional deficiencies characterized by decreased weight will further aggravate the condition of anemia itself.[14-16]

In this study, there was a significant improvement of Hb level from before therapy (11.89 ± 1.77 g / dL) compared with after therapy (13.29 ± 1.80 g / dL). This is also evident from the increase in erythrocytes cells initially amounting to 4.61 ± 0.71 x106 / uL to 4.87 ± 0.56 x 106 / uL although this increase was not statistically significant. In addition, the hematocrit value also increased significantly from 36.61 ± 0.56 vol% to 40.71 ± 4.63 vol%.

From this study seen anemia anemia improvement from before therapy compared with after therapy. Increased levels of hemoglobin, increased red blood cell count and increased hematocrit showed improvement in anemia caused by decreased inflammation in patients with MDR lung disease resulting in improved clinical appetite and improved body weight. Nutritional deficiencies are resolved will help the body to increase hemoglobin production along with better heme formation.[17]

The MDR regimen ATD regimen was shown to have no effect of drug suppression on the erythropoiesis process so that Hb levels, erythrocytes and hematocrit levels were corrected after the patients were treated. This is in contrast to the results reported by Muzafar et al in 2008 and Kassa et al in Ethiopia in 2016, where anemia occurs after ATD therapy. This may be due to the absence of rifampicin as one of the MDR regimen ATDs. Rifampicin is an ATD that has hemolytic side effects on red blood cells resulting in a decrease in Hb and erythrocyte count. However, in the pulmonary TB pulmonary TB therapy, rifampicin is excluded as it has become resistant, thus giving no antimicrobial effects to M. tuberculosis.[6,9,18]

From the leukocyte profile in this study, it can be seen that there is significantly decreasing of leukocyte count than before therapy compared with receiving MDR regimen ATD therapy. From the leukocyte count, most of the changes are not significant except the increase of eosinophil and lymphocyte percentage, decrease of granulocyte and monocyte count and increase of lymphocyte count. This means that there is a change during therapy in the form of decreased acute infection resistance process and M. tuberculosis infection and increased lymphocyte response as cellular immunity. Before patients get treatment, M. tuberculosis infection will increase the number of monocytes in response to high mortality of macrophages due to high macrophage toxicity of M. tuberculosis. In addition, M. tuberculosis infection will also lead to the easy co-infection of non-specific bacteria that cause the body to react by increasing the amount of granulocytes to fight such acute infection. However, after MDR lung TB patients received therapy, the deaths of M. tuberculosis and non-specific bacteria will decrease the percentage of monocytes and granulocytes offset by increased lymphocytes as cellular immune responses. In addition, there is no MDR regimen ATD that can suppress leukopoiesis process. The results of this study differ from those of Nagayama et al in 2014 and Maartens et al. From a 1990 South African study showing leucopenia after taking ATD. The results of Yaranal et al in India in 2013 are also different from the results of this study where no leukocytosis occurs in patients receiving MDR-regulated ATD therapy. The absence of the use of medications other than the MDR regimen ATD may be the reason for no significant change in leukocyte images and their counts.[5,7,8,20]

The results of this study also showed a significant change of platelet count where there was a decrease in platelet count from 366.24 ± 141.21 to 295.47 ± 108.09 (P-value 0.002). These results are similar to studies in India and Ethiopia where there is a decrease in platelet counts after taking ATD. Reduced platelets can be caused by the effects of ATD and platelet destruction due to immunity. ATD rifampicin and isoniazid have been known to cause thrombocytopenia. Rifampicin-related antibodies can attach to platelets and cause destruction, whereas the mechanism of INH causes thrombocytopenia remains unclear. However, in our study, rifampicin and INH were no longer used as ATD in the MDR regimen because it has shown resistance to M. tuberculosis, it can be concluded the cause of the decline in platelet levels after taking ATD MDR regimens is immune-related platelet destruction.[21,22]

Changes in MCV and RDW-CV were also statistically significant in our study (P-value 0.010 and 0.038) where prior to treatment the mean MCV was 80.03 ± 8.40 and rose to 83.97 ± 7.67 and the initial RDW-CV was 14.7 ± 2.24 and decreased to 13.43 ± 1.63. This result is directly proportional to the increase in Hb which also occurs in our study. MCV, MCH, MCHC, and RDW-CV are an index of erythrocyte conditions in the blood.

Increased MCV and decreased RDW-CV states that there is an increase in Hb levels. These results indicate that the use of MDR regimen ATD does not cause anemia due to the absence of rifampicin and INH in the MDR regimen.[23,24]

CONCLUSIONS

There were significant changes in hemoglobin, hematocrit, platelet count, red blood cell distribution range, corpuscular volume, the percentage of eosinophils and lymphocytes, and number of granulocytes, lymphocytes, and monocytes after treatment of antituberculosis drugs MDR regimens that generally occurred significantly in the male sex and in the age group of 45-60 years.

Increased hemoglobin levels with increased hematocrit, average corpuscular volume and decreased the range of red blood cell distribution showed that MDR regimen ATD therapy did not cause anemia for its users. The decline in platelet counts was also not affected by the administration of MDR regimen ATD therapy but suspected to be caused by immune-related destruction. While there was no significant change in the number of leukocytes, only a change in the type count indicates that acute infection changes to normal after therapy.

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