



## Overview and Management of drug withdrawal tuberculosis patient

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### ABSTRACT :

Drug-resistant tuberculosis (DR-TB) is still a threat in TB control and is a problem major public health issue in many countries around the world. One of the main causes is a history of withdrawal from anti-tuberculosis drugs in TB patients. This article aimed to present the overview and management of TB patient with anti-tuberculosis withdrawal history. A 48 year old woman came in Emergency Room with shortness of breath that had been increasing for an hour before entering the hospital. Shortness of breath was felt when the patient was resting and increased with activities, and shortness of breath did not decrease even if while resting. The breathlessness was accompanied with purulent cough. The results of the history, physical examination and supporting examinations strongly support the diagnosis of drug withdrawal pulmonary TB. The conclusion is tuberculosis patients who experience drug withdrawal like the patient above will most likely become Drug-resistant tuberculosis (DR-TB) patient.

Keywords: Withdrawal Anti Tuberculosis Drugs, Resistant, Treatment

### 1. BACKGROUND :

Tuberculosis (TB) is a disease caused by *Mycobacterium Tuberculosis* (M.TB) complex infection. In general, the characteristics of Tuberculosis bacteria (*Mycobacterium Tuberculosis*) include being rod-shaped with a length of 1-10 microns, a width of 0.2-0.6 microns.<sup>1</sup> Most of the bacteria walls consist of fatty acids (lipids) and peptidoglycan. This lipid is what makes these bacteria resistant to alcoholic acids so they are called acid-resistant bacteria, resistant to chemical disturbances. Bacteria appear in the form of red rods when examined under a microscope. This microorganism are resistant to low temperatures so they can survive for long periods at temperatures of 40 C to minus 700 C. This bacteria is very sensitive to heat, sunlight and ultraviolet light. Direct exposure to ultraviolet light will make the bacteria die within a few minutes. However, inside the phlegm at a temperature of 30-37 degrees Celsius M.TB will die in approximately 1 week. This bacteria can be dormant (sleeping/not developing). Apart from that, M.TB is also aerobic, so they prefer tissues that have a high oxygen content. In the lungs, the part that is rich in oxygen is in the apical area, so this area is a predilection site for tuberculosis.<sup>2,3,4</sup>

The source of transmission is through small droplets of smear positive TB patients phlegm. However, this does not mean that smear negative TB patients do not contain M.TB in their phlegm. This can occur because the number of germs contained in the test sample is <5000 germs/cc of phlegm, making it difficult to detect through direct microscopic examination. TB patients with negative smears also still have the possibility of transmitting TB disease. The transmission rate of smear-positive TB patients is 65%, while smear-negative TB with positive culture results is 26%, while TB with negative culture results and positive chest x-rays is 17%. Infection will occur if another person inhales air containing infectious phlegm.<sup>5,6</sup>

When coughing or sneezing, patients spread the bacteria into the air in the form of droplet nuclei. One cough can produce around 3000 splashes of phlegm.<sup>4</sup> Transmission of this disease is mostly from the air (air borne spreading) through inhalation of droplet containing nuclei of bacilli, especially those obtained from pulmonary TB patients who cough up blood or phlegm containing acid-fast bacilli (BTA).<sup>5</sup> When the germs are coughed up they become droplet nuclei in the air. These particles will remain in the open air for 1-2 hours depending on the presence or absence of ultraviolet light, poor ventilation and humidity. In a humid atmosphere, these bacteria can survive for months. Then these particles are inhaled by healthy people and will stick to the airways or lung tissue. These particles can enter the alveoli because their size is <5 micrometers.<sup>6</sup>

Once in the alveolar membrane, usually in the lower part of the upper lobe of the lung or the upper part of the lower lobe of the lung, these bacteria cause an inflammatory reaction. The M.TB will first be encountered by polymorphonuclear leukocytes and phagocytize them but do not kill them. During this period, TB bacilli multiply freely, both extracellularly and intracellularly in the cells that phagocytize them. After 3 weeks, the phagocytosed TB bacilli will be digested by macrophages, generally die and be expelled by macrophages from the tracheobronchial tree along with the ciliary movement of their secretions. Virulent bacilli will remain alive and if the body's defenses are weak, non-virulent bacilli will also remain alive.<sup>6</sup> After that, the germs will lodge in the lungs and form a pneumonic nest called the primary nest or primary affect (ghon focus).<sup>6</sup> This primary nest can occur in any part of the lung tissue. If it spreads to the pleura, it can cause pleural effusion, apart from that, M.TB can also enter the gastrointestinal tract, lymph tissue, oropharynx, skin, regional lymphadenopathy occurs, then the bacteria enter the veins and spread to all organs such as the lungs, brain, kidneys and bone. If it enters the pulmonary artery, it can spread to all parts of the lung to become miliary TB.<sup>7</sup>

TB patient with dropping out of treatment is patients who have not received treatment for 2 consecutive months or more before the treatment period is complete (RI Ministry of Health, 2011). The consequences of dropping out of treatment are: patients can be resistant to the drug (MDR=Multi Drugs Resistant), so that *Mycobacterium* bacteria which causes tuberculosis become resistant against drugs and is said to be a bacteria killer mass. WHO

estimates that this bacteria has kills around 2 million people every year. Between 2002-2020 it is estimated that around 1 billions of people will be infected.<sup>2</sup> In other words the increase in the number of infections is more than 56 million people every year. If the calculation is carried out, The number of TB patients will increase around 2.8-5.6 million people every year, and 1.1-2.2 Millions of people die every year from TB. The Indonesian Ministry of Health estimates that every year Indonesia recorded 429,730 new cases of TB with death rate 62,246.<sup>4,5</sup>

The high TB morbidity rate is influenced by several things that complicate TB control efforts, one of which is the incidence of drug withdrawal. Pulmonary TB drug withdrawal events will give rise to new problems such as resistance to anti-tuberculosis drugs.<sup>2</sup> In addition, incomplete treatment will increase the risk of transmission, reduce productivity, increase the death rate, and increase the number of MDR-TB whose treatment takes longer to treat with a larger amount of medication.<sup>3,5</sup> This article aimed to present the overview and management of TB patient with anti-tuberculosis withdrawal history.<sup>4,5</sup>

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## 2. CASE PRESENTATION

A 48 year old woman came in Emergency Room with shortness of breath that had been increasing for an hour before entering the hospital. Shortness of breath was felt when the patient was resting, and shortness of breath did not decrease even if while resting. The breathlessness increased when carrying out activities. Previously, the patient had felt shortness of breath for three months, came and went. The patient also had cough since three months ago, and the cough was then accompanied by shortness of breath, coming and going accompanied by white to greenish phlegm. There was also fever, especially at night. Patient felt night sweats since three months ago and decreased appetite. She felt that there was weight loss. The patient said that there was history of using Anti tuberculosis drugs one year ago but was not completed, and received streptomycin injections but decided to stop getting the medicine on her own. The patient was treated for pulmonary TB at Yarsi Hospital and Dr. M djamil Hospital Padang. The patient lives with her children and husband. Physical examination of the anterior and posterior lungs was found on normochest inspection symmetrically in left and right chest, on palpation was found that fremitus was the same in left and right chest, percussion was found sonor and by auscultation, it was found vesicular breath sounds and smooth wet rhonki in the right and left chest. In laboratory examination, it was found that haemoglobin 11.4 gr/dl, Hematocrite 34.9%, leukocytes 10910/mm<sup>3</sup>, platelets 427000/mm<sup>3</sup>, From the Chest x-ray examination with duplex pulmonary TB impression and BTA examination was found positive three, LED was 100 mm.<sup>3</sup> The results of the history, physical examination and supporting examinations strongly support the diagnosis of drug withdrawal pulmonary TB.

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## 3. DISCUSSION

Symptoms of tuberculosis can be divided into general symptoms consisting of systemic symptoms, namely weight loss, subfebrile fever, night sweats, and decreased appetite. Secondly, there will be respiratory symptoms such as cough, sputum, coughing up blood, and chest pain. The symptoms above can also occur in other diseases, the most important thing is that the symptoms in tuberculosis will increase gradually over weeks to months. Early in the disease, the signs and symptoms of tuberculosis are often nonspecific and hidden. In most cases, complaints of cough will appear, at first it is unproductive then the cough will be prolonged (more than two weeks) and is followed by purulent phlegm, and sometimes accompanied by blood in several patients.<sup>8,9,10</sup> At the beginning of the disease, if only by physical examination, it will be very difficult to show abnormalities in the lungs. Some abnormalities that can be found on physical examination include bronchial breath sounds, amphoric breath sounds, wet crackles, and weakened breath sounds.<sup>11,12</sup> The location of the abnormalities is usually found in the upper lobe area and can be widened to other part of the lungs. The crackles and bronchial breath sounds indicate the presence of consolidation.<sup>13</sup>

The initial suspicion of pulmonary tuberculosis is the presence of an abnormal chest radiograph in a patient with respiratory symptoms. Although the classic picture is usually an abnormality such as a cavity or infiltrate in the upper lobe area, any radiographic pattern can be found ranging from a normal picture to a diffuse infiltrate. Microscopic examination, especially staining sputum with acid-fast bacilli is the main test in establishing the diagnosis of tuberculosis.<sup>14</sup> Sputum examination to confirm the diagnosis is carried out by collecting sputum at any time in the morning on two consecutive patient visits. The patient was treated with Anti Tuberculosis drugs category II.<sup>5</sup>

In several studies, it was found that motivation to recover was the most influential factor in maintaining compliance with treatment for TB patients, followed by the role of the family in second place and the role of health workers and Medicine Taking Supervisor (MTS) in last position.<sup>6</sup> Apart from that, there are also studies that shows that the role of MTS has a significant influence on the treatment behavior of pulmonary TB patients. Age factors such as productive age (15-55 years), gender, education level, employment status, and affordability of health facilities influence the causes of someone experiencing drug withdrawal in long-term TB treatment. Based on research conducted in Riau, there was a significant relationship between age and the incidence of dropping out of pulmonary TB treatment, where productive age increased the risk of dropping out of pulmonary TB medication by 3.5 times. This can be related to busyness at work and the ability to withstand clinical symptoms that have improved.<sup>14</sup>

The World Health Organization implements DOTS strategy (Direct Observation Treatment Short Course) in the management of TB patients to ensure the patient swallows the medication, carried out direct supervision by a person or Medicine Taking Supervisor (MTS). There is supervision and efforts to streamline treatment time span, it is hoped that pulmonary TB sufferers will take medication regularly so that TB treatment can be carried out completely. Tuberculosis patients who experience drug withdrawal like the patient above will most likely become Drug-resistant tuberculosis (DR-TB) patient. Resistance of *Mycobacterium tuberculosis* (M.TB) caused by spontaneous mutations in chromosomes. Proportion of germs that has undergone mutations (wild-type resistant mutants) in patients who have never received Anti Tuberculosis drugs (ATD) is very small, mostly this condition happens in Tuberculosis patients with drug withdrawal history. TB treatment causes selective barriers in the population of M.TB germs so sensitive M.TB germs are killed, temporarily the mutant population will reproduce and cause this to occur resistance to Anti Tuberculosis drugs (acquired resistance).<sup>2,15</sup>

The treatment strategy for DR-TB patients is to ensure all patients who have been confirmed as MDR TB can access treatment quickly, according to standards and quality. The drug mix for DR-TB patients consists of ATD first line and second line. The ATD mixture can be adjusted if there is a change in the results of the M. Tuberculosis susceptibility test. ATD Decision and replacement is determined by the DR-TB clinical expert team. All DR-TB patients need to undergo an initial examination, examinations during treatment until completion treatment, and examination after completion of the treatment period. Initial preparation for treatment includes supporting examinations which aims to determine the initial conditions of various functions organs (kidneys, liver, heart), electrolyte examination, and various other laboratory tests. Examination during TB treatment aims to monitor treatment progress and drug side effects. DR-TB treatment must be started within 7 days

after the patient's diagnosis is established. Treatment for patients with drug resistant is given on an outpatient basis (ambulatory) from the start and supervised every day directly by the Medicine Taking Supervisor (MTS). In accordance with WHO recommendations in 2020, treatment, DR-TB in Indonesia currently uses a drug-free mixture injection, which is divided into two, namely a combination of short term treatment (9–11 months) and long term treatment (18–20 months). Determining the treatment guidelines for drug-resistant TB patients is based on various criteria and patient conditions.<sup>5</sup>

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## Conclusion

Tuberculosis patients who experience drug withdrawal will most likely become Drug-resistant tuberculosis (DR-TB) patient. Management of DR TB is much more complex and difficult than ordinary TB cases. DR-TB patients will receive Anti Tuberculosis Drugs longer and their clinical conditions will also be more severe.

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## Conflict of Interest

No potential conflict of interest relevant to this article was reported

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