



# ***Mycobacterium tuberculosis* Involvement in Tetralogy of Fallot: A Case Report of Tetralogy of Fallot Patient with Pulmonary Tuberculosis in A Tertiary Health Care in Indonesia**

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## **Abstract**

**Background:** Pulmonary tuberculosis in patients with congenital heart disease is a rare case and remains challenging to diagnose and treat. This study aimed to emphasize the association between pulmonary tuberculosis infection and management in patients with congenital heart disease.

**Case:** This case study presents 18-year-old male with Tetralogy of Fallot (ToF) who had pulmonary tuberculosis. The tuberculosis diagnosis was confirmed clinically, followed by positive IGRA. The patient underwent standard care within the hospital and upon discharge, he was prescribed with standard anti-tuberculosis regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) for a week then discontinued it. After 3 months the patient initiated intensive phase (RHZE) for 2 months and followed by 4-month maintenance phase of Isoniazid and Rifampicin. Immediate evaluation showed improved patient's chest radiography and symptoms' remission. This study presented provisioning therapy regimen and nutritional care delivery for pulmonary tuberculosis patient with ToF. Further patient's clinical evaluation suggested a substantial recovery process. The patient prescribed with infection control and dietary management upon hospital discharge. Counseling to improve patient's knowledge was performed to prevent recurrent TB. Collaborative care established between internal medicine specialists, cardiologist, pulmonologist, and clinical nutritionist appeared to be effective to promote patient's recovery and quality of life (QoL).

**Conclusion:** Appropriate management of cases improves patient outcomes and QoL. Early screening, diagnosis and treatment should be introduced regardless of the patient's clinical status. Adequate support from the patient's family and relatives are required to eliminate TB infection.

**Keywords:** collaborative care, congenital heart disease, pulmonary tuberculosis, tetralogy of Fallot

## INTRODUCTION

Tuberculosis remains in the top list of common infectious diseases that pose threat to death despite advanced development of diagnosis and treatment.<sup>1,2</sup> Tuberculosis patients are frequently associated with congenital heart disease (CHD) due to increased pulmonary circulation compared to normal people.<sup>3-5</sup> Because of the nature of the disease, clinicians experienced difficulties in diagnosing tuberculosis which led to prolonged treatment or improper intervention.<sup>6</sup>

Patients with CHD are at higher risk for developing respiratory tract infections. Recurrent infection may occur and among frequent cases is pneumonia. Current evidence indicated that the risk for pulmonary tuberculosis remain unclear among pediatric cases as well as its associated complications.<sup>3</sup>

Classification of congenital heart diseases are based on the blood flow. Patients are grouped into cyanotic-CHD and acyanotic-CHD. Patients with acyanotic-CHD more susceptible to tuberculosis infection due to increased respiratory blood flow. Nevertheless, studies reported rare occurrence of pulmonary TB in patient with Tetralogy of Fallot (TOF) which categorized as a cyanotic-CHD characterized with decreased pulmonary blood flow.<sup>2,4</sup> Less blood volume in the lung causing delayed growth of *Mycobacterium tuberculosis*. Contrary, patient with normal or increased pulmonary

blood flow are prone to provide suitable environment for the bacteria to replicate.

Pulmonary tuberculosis in CHD patient are rare cases, especially in the cyanotic-CHD patients. The screening, diagnosis, and treatment of these cases remain challenging. Due to the extremely rare and challenging management of this case, we presented a case of 18-year-old male patient diagnosed with TOF and pulmonary tuberculosis. Treatment regiments and intervention history were given to illustrate the day-to-day basis care. The case discovered in a tertiary care hospital in Java Island, Indonesia. Currently Indonesia is the third contributor of tuberculosis cases globally with frequent TB-HIV (human immunodeficiency virus) coinfection, and multidrug-resistant TB (MDR-TB).<sup>7</sup>

## CASE

An eighteen-years-old male patient admitted to the hospital with TB symptoms on October 21<sup>st</sup>, 2021. The patient reported hemoptysis around 10 to 20 mL, impaired mucus excretion and breathing pattern at the time of admission. He experienced insomnia, significant weight loss and cough history in the past two months with nausea. No history of contact with positive TB cases. His past medical history indicated a delayed motoric development. Patient was able to communicate fluently in the age of 5.

During his treatment, he was not supported by his parents. The patient was living with his grandparents who actively

encouraged him to seek for medical care. He had no socioeconomic issue regarding health seeking behavior.

His body weight was 40 kg with 170 cm height, BMI 13.77 and categorized into undernourished. At the initial assessment, his respiratory rate was 26 times/minute, heart rate 130 BPM, blood pressure 130/70 mmHg and 36.9 body temperature. The patient's oxygen saturation was 84% and maintained to 92-93% with 4 lpm flow on nasal cannula.

Patient's general appearance was poor, indicated by weakness, breathlessness, and underweight. From the pulmonary examination found that fremitus tactile and the vesicular sound higher on the left lung. No abnormalities observed from the head, neck, abdominal, and extremity examination.

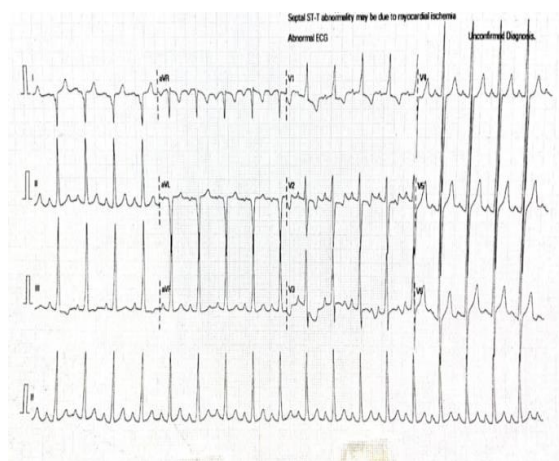


Figure 1. Patient's Electrocardiogram on Oct 2<sup>nd</sup>, 2021

From the cardiac examination found cardiomegaly. Auscultation test confirmed S1 normal, S2 single but noisy, PSM 3/6 at LPSS SIC III-IV, murmur ejection 3/6 at SIC II LPSD.

Blood examinations results indicated hemoglobin level of 14.8 gr/dL, WBC

20.72/mm<sup>3</sup>, neutrophil 85.8% and lymphocyte 7.7%. Patient's partial thromboplastin time (PTT) was 19.6 while APTT was 42.5. The INR was 1.39 and D-Dimer 715. CRP test yielded result 116 ng/ml and LDH 261 U/L.

The patient was diagnosed with tetralogy of Fallot with MAPCAS to the right lung in July 2018. Previous echocardiography examination concluded TOF with pulmonary atresia, collateral, and mild TR. The electrocardiogram indicated RAD RAE RVH with ST depressed at V1-V3.

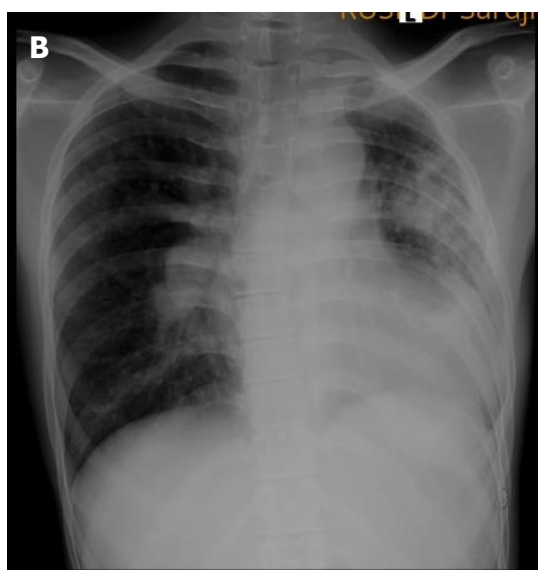
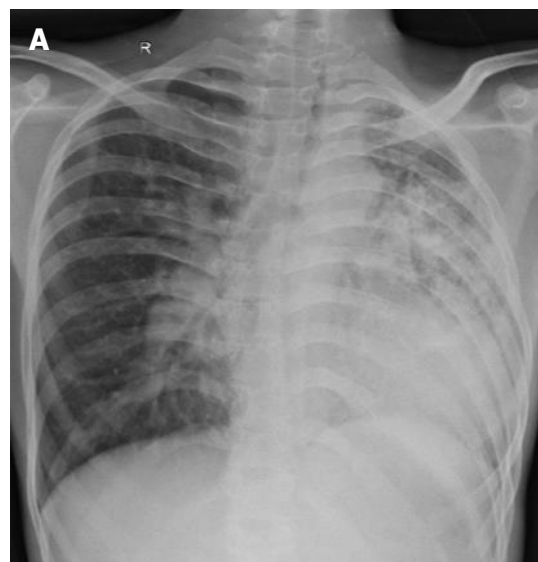


Figure 2. A) Chest X-Ray Before and B) After 2 Months TB Treatment

The Interferon Gamma Release (IGRA) tuberculosis blood test was positive, indicated the patient was infected with pulmonary TB. Neither TCM/AFB test was carried out due to difficulties in sputum sample collection. Additionally, the patient had recurrent hemoptysis, therefore IGRA test was performed as an alternative. Recurrent TB infection occurs due to lack of TB treatment adherence. On August 2021, the patient was prescribed for anti-TB regimen but didn't manage to follow the therapy. He took the medicine for a week and discontinued it. Further intervention during the hospital admission ensures the patient comply to the standard TB regimen (2RHZE/4RH).

Patient was admitted for severe malnutrition programme. The total calories prescribed was 1700 kcal with 70 g protein. He planned for a high energy and high protein diet with ONS F75 2X200 cc. Parenteral nutrition in a composition of lipid emulsion, amino acids, electrolytes, and glucose were programmed for 1000 mL/24h.

## DISCUSSION

Despite the advances in tuberculosis diagnosis and treatment, around 450.000 children died because *M. tuberculosis* infection. The prevalence of TB cases among children aged 0-15 reached 1.3 million in 2021.<sup>8</sup> Low and middle-income countries are being burdened by these issues due to poor environmental status, lack of nutrition for children, inadequate immunization, and HIV infections.<sup>5</sup>

Tuberculosis management in children poses a unique challenge compared to adults. 65% of pediatric patients initially didn't develop tuberculosis's symptoms and only able to be validated with radiology.<sup>9,10</sup> Children with positive radiological findings are prone to recurrent infection during their adulthood.<sup>11</sup>

Chest X-Ray features of active primary pulmonary TB are primary (Ghon) focus which can be seen as calcified nodule with or without mediastinal lymph node enlargement, perihilar lymph nodes enlargement, pneumonic consolidation, cavitation, miliary opacities, pleural effusion, or pulmonary edema.<sup>12</sup> Meanwhile the CXR finding of inactive TB are fibrosis, persistent calcification (Ghon's focus), and/or tuberculoma. CXR findings of secondary TB in adults are patchy consolidation with cavitory lesion or coarse reticulonodular densities which usually involve the upper lobe.<sup>13</sup> Proportion of the affected area of the pulmonary lobes determine the case mortality.

In this case report, we presented a patient with clinically confirmed tuberculosis infection with tetralogy of Fallot and malnutrition. Malnutrition is common in patient with CHD, especially in developing country like Indonesia. Based on some research malnutrition happens in more than half of patients with CHD. Malnutrition happens in CHD because of decreased intake, increased demands, or both. Underweight is the combination of acute and chronic malnutrition. Underweight can lead to secondary immunodeficiency which increases the

susceptibility to infection, including tuberculosis. Either protein-energy or micronutrients deficiencies can increase the risk of tuberculosis infection.<sup>14,15</sup>

Prevalence of tuberculosis is higher in CHD patients than normal population. A retrospective study indicated CHD patients, especially cyanotic-CHD, are at 2.5x higher risk of TB. Higher incidence of TB also found in patient with increased pulmonary circulation i.e., transposition of great arteries and acyanotic-CHD, like ASD and VSD.<sup>3,16</sup>

Previous cases of CHD and pulmonary tuberculosis was also reported in Sonipat, India. A 21-year-old male suffered from CHD reported complaints bloody cough, dyspnea, and other symptoms such as fever, loss of appetite, weight-loss, abdominal pain, and icterus. He was diagnosed with pulmonary tuberculosis after sputum examination with cartridge based nucleic acid amplification test. He was put on alternate tubercular regimen, as his liver function worsened. Even though the regimen was consumed regularly, he still reported persistent dyspnoea and suspicion of pulmonary embolism. CT pulmonary angiography was done, and there is no evidence of arterial thrombosis. From the CT scan found complex cardiac congenital anomaly.<sup>3</sup>

Recent development in testing kit and widely distributed capable healthcare centers allow enhanced diagnosis process of pulmonary tuberculosis in patient with CHD<sup>14</sup>. A study reported that among pediatric patients with normal immune system, 10% of them diagnosed with TB-

positive culture. Tuberculin Purified Protein Derivative (TU PPD) test generated variance in the test results. Multiple factors associated with TU PPD validity to diagnose TB, such as age, nutritional status, bacterial load, and MTB count. Patients with low albumin level tend to show negative results.<sup>10</sup>

The sensitivity of PPD/TST/Mantoux test among pediatric patients was around 63% based on a report.<sup>17</sup> In Indonesia, screening for tuberculosis utilizing PPD in primary care remains limited. It leads to delayed treatment administration and causes poor clinical outcome.

Considering its low sensitivity, PPD doesn't serve reliable diagnostic tool to diagnose tuberculosis.<sup>17</sup> In children  $\geq 5$  years old, IGRA has greater sensitivity than PPD and should be considered the preferred immunodiagnostic test.<sup>18</sup> The gold standard to diagnose tuberculosis is culture examination, followed by species identification and drug sensitivity testing.<sup>19</sup> WHO recommends bacteriologic diagnostic for adult's patient despite it taking 2-8 weeks to complete. Nevertheless, for pediatric population bacteriological confirmation is achievable in  $<50\%$ ; in such cases pulmonary TB is diagnosed by other clinical criteria or other examination modality.<sup>20,21</sup>

Either IGRA or PPD can be used to diagnose LTBI. PPD is one of the components in pediatric tuberculosis scoring system. Based on WHO guidelines, PPD still can be used to diagnose pediatric tuberculosis. PPD is considered safe and preferred over TB blood tests for children



less than 5 years old.<sup>22</sup> IGRA are more specific than PPD, but it hasn't been found to perform better than PPD. Although bacteriological confirmation of TB in children isn't always feasible, it should be sought whenever possible by microscopy, culture or TCM.<sup>20,22</sup>

Culture examination isn't the only one modality to diagnose TB. The other current modalities including BACTEC, ELISA, PCR, and Real Time-PCR (RT-PCR) are shown to be valid and reliable too. RT-PCR provides the fastest test result. However, it has low sensitivity (56%) and high specificity (97%) in pediatric tuberculosis.<sup>2,23</sup> Despite laboratory tests demonstrating effectiveness for diagnosis, it remains important to establish clinical case definitions based on physical examinations.

In 2019, WHO reported that 12% of all TB cases globally represented by children, 32% by adult women, and 56% by adult men.<sup>24</sup> According to the systematic review and meta-analysis performed by Charan et al in 2019, that prevalence of MDR-TB in newly confirmed cases was 3% and in the previously treated cases were 35%. The pooled proportion of MDR-TB confirmed in new cases group using BACTEC method was 21%; while with Alamar blue dye reduction assay was 5%; and MIC method was 1%.<sup>25</sup>

The study also indicated pooled proportion of confirmed MDR-TB among previously treated cases group using BACTEC method was 58%; the genotype MTB DR plus assay method 19%; RNTCP guideline 28%; the absolute concentration method 53%; the resistance ratio method

was 8%; Alamar blue dye reduction assay 16%; MIC method 26%; and using Lowenstein Jensen method was 72%. In the other hand, according to the WHO Global TB Report of 2020, about 3.4% (95% CI, 2.5–4.4%) of new cases and 18% (95% CI, 7.6–31%) of previously treated cases had MDR/RR-TB from all age groups.<sup>25</sup>

Drug-resistant TB (DR-TB), especially MDR-TB, remains a threat for both children and adults. More than 30,000 children diagnosed with MDR-TB, globally. According to the systematic review and meta-analysis by Song et al. in 2021, from the 23,652 children with TB, there are 13.59% with DR-TB; 3.72% with MDR-TB; 6.07% with mono-resistant TB; 1.61% polydrug resistant TB, and 0.44% with extensively drug-resistant TB. DR-TB diagnosis in children remains challenging because bacteriological confirmation of pulmonary TB yield in no more than 40% of children and even less frequently for extrapulmonary TB.<sup>26</sup>

## CONCLUSION

Patients with acyanotic-CHD have a higher risk of TB infection due to higher blood circulation in the pulmonary tissue and malnutrition condition. Appropriate management of cases improve patient outcomes and quality of life. Suspicion of pulmonary TB is supposed to be maintained among patients with CHD. Early screening, diagnosis and treatment should be introduced regardless of the patient's status. Family members and significant

others requested to limit the exposure to TB infection by implementing appropriate preventive measures.

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