



## Challenge in diagnosing tuberculosis on a boy with severely wasted in limited resource area

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### ABSTRACT

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Hunger and malnutrition are still the leading cause of morbidity and mortality among children around the world. Undernutrition increases the risk of tuberculosis (TB) which in turn could worsen undernutrition. Indonesia is currently the second highest newly diagnosed TB in the world after India. TB in children with severely wasted is difficult to diagnose. This is a case report about a 35-month-old boy with severely wasted complicated with hypoglycemia, severe dehydration, and pneumonia. After proper nutritional management without the expected outcome, patient was then worked up for TB resulting negative result of tuberculin skin test (TST). Nevertheless, he was still treated with antituberculosis and had significant improvement, hence continuation to complete 6 mo period of therapy. This case report describes the challenge of diagnosing TB in children with severely wasted in limited resource areas. The reduced immune responses, due to severely wasted, caused subtle clinical signs of TB and decreased sensitivity to tuberculin testing. The unavailability of radiologic examination added further problem in diagnosis. The diagnosis of TB should be considered among children in areas with a high prevalence of TB, presenting with severely wasted refractory to proper nutritional management.

### ABSTRAK

Kelaparan dan malnutrisi masih menjadi penyebab utama morbiditas dan mortalitas anak-anak di seluruh dunia. Kekurangan gizi dapat meningkatkan risiko terjadinya tuberculosis (TB) yang pada gilirannya dapat memperburuk kekurangan gizi. Saat ini Indonesia menduduki peringkat kedua tertinggi penderita TB baru di dunia setelah India. Tuberkulosis pada anak gizi buruk sulit didiagnosis. Pada makalah ini dilaporkan kasus anak laki-laki berusia 35 bulan keadaan gizi buruk dengan komplikasi hipoglikemia, dehidrasi berat, dan pneumonia. Setelah manajemen nutrisi yang tepat tanpa hasil yang diharapkan, pasien kemudian diperiksa untuk TB dengan hasil tes kulit tuberkulin (TST) negatif. Namun demikian, ia masih diobati dengan antituberkulosis dan mengalami peningkatan berat badan yang signifikan, sehingga dilanjutkan untuk menyelesaikan periode terapi 6 bulan. Laporan kasus ini menjelaskan tantangan dalam mendiagnosis TB pada anak dengan kondisi gizi buruk di daerah dengan sumber daya yang terbatas. Berkurangnya kekebalan tubuh, karena kondisi gizi buruk, menyebabkan tanda-tanda klinis TB yang tidak jelas dan penurunan kepekaan terhadap tes tuberkulin. Tidak tersedianya pemeriksaan radiologis menambah masalah lebih lanjut dalam diagnosis. Diagnosis TB harus dipertimbangkan di antara anak-anak di daerah dengan prevalensi TB yang tinggi, dengan gejala yang sangat refrakter terhadap manajemen nutrisi yang tepat.

### Keywords:

severely wasted;  
tuberculosis;  
pneumonia;  
malnutrition;  
children

## **INTRODUCTION**

Hunger and malnutrition are still the leading cause of morbidity and mortality among children around the world. The Sustainable Development Goals (SDGs) seek sustainable solutions to end hunger and all forms of malnutrition by 2030 and achieve food security. Nutritional problems, such as malnutrition and stunting, are still major problems that need to be addressed immediately.<sup>1</sup> In 2019, 47.0 million children under five years around the world were wasted, of which 14.3 million were severely wasted and 10.5 million of severely wasted cases occurred in Asia.<sup>2</sup> According to Basic Health Research (Riset Kesehatan Dasar, Riskesdas) 2018, the proportion of children under five years in Indonesia (0-59 mo) is around 8.8% (23 million), and 3.5% (805,000) children are severely wasted. The prevalence of severely wasted in Papua is 4.8%.<sup>3,4</sup> Based on Statistic Data of Papua 2020, incidence of wasted in Pegunungan Bintang Regency were 110 cases.<sup>5</sup>

Wasting has short and long-term impacts, such as growth and development disorders, including cognitive dysfunction, impairment of the immune system function, risk of degenerative disease later in life, and ultimately death. The risk of death associated with severe wasting is 12-fold higher compared to the well-nourished children.<sup>6,7</sup> Children with undernutrition are at increased risk of death from infectious diseases and, conversely, severe infectious diseases in early childhood can affect nutritional status. Undernutrition is also known to increase the risk of tuberculosis (TB) and TB can cause or worsen undernutrition.<sup>8</sup>

There were estimated 10.0 million new cases of TB disease in 2019 globally (130 cases per 100,000 population, and about 845,000 new TB cases in Indonesia (312 per 100,000 population). The number of new TB cases in Indonesia was the second highest after India.

Prevalence of TB in Papua based on Basic Health Research 2018 was 0.77%. This number was higher than national average. TB affects all countries and age groups whereas 12% were children.<sup>4,9,10</sup>

According to Indonesian national guideline of medical service for management of TB 2019, the diagnosis of TB in children based on history, symptoms, physical examination include analysis of child development, tuberculin test or IGRA (interferon gamma release assay), bacteriological confirmation and other relevant investigations (chest X-ray, lumbar puncture, biopsy and others according to the location of the affected organ).<sup>9</sup>

Diagnosis of TB among children utilizes a scoring system that can be carried out in limited health care facilities, both with limited medical personnel and diagnostic tools. If the microscopic examination is negative or there is no access to referrals (radiology/Xpert MTB/RIF/culture), then broad-spectrum antibiotic therapy (non-OAT and non-quinolones) should be administered for 1-2 wk. If there is no clinical improvement after antibiotic administration, the patient needs to be assessed for TB risk factors. Patients with high risk factors for TB can be diagnosed as clinical TB. Since the higher risk of disseminated TB in children less than 5 y.o., TB therapy should be given as soon as the diagnosis is made.<sup>9</sup>

The bacteriological diagnosis of TB in children is more difficult due to low production of sputum. The diagnosis of TB among children in limited resource area both with limited medical personnel and diagnostic tools is even more difficult. Clinical signs of TB in children are largely non-specific, such as unexplained weight loss or failure to grow normally, chronic cough, unexplained fever, especially when it continues for more than 2 wk.<sup>11</sup> Clinical signs of TB in children, especially those with severely wasted, are often subtle. The diagnosis of TB is even more

difficult when such children present with acute pneumonia.<sup>12</sup> Following below is a case report of Pulmonary TB in a boy with severely wasted presented with pneumonia.

## CASE

A 35-mo.o. Papuan boy, presented to the emergency room (ER) of Oksibil General Hospital with chief complaint of difficulty of breathing over the last 48 h. Patient had history of three weeks of watery diarrhea, twice to three times over 24 h, slightly greenish stools with no blood noted. Diarrhea was associated with 3 wk cough and intermittent fever. Patient was noted to get weaker by day and drink poorly. The symptoms persisted until two d prior to admission, he had difficulty of breathing. There was no history of vomiting. His urination was within normal limit. There was no history of pain during urination or bloody urine.

The patient was the youngest of three siblings. One year ago, the patient was admitted to our institution with community-acquired-pneumonia. His weight and height at that time was 8 kg and 82 cm. The patient was discharged fully recovered after seven d of treatment with antibiotics and since then had never come for follow up and/or seeking any treatment at our institution. The patient had never been evaluated for TB, and both parents denied any history of TB, prolonged coughing, or TB treatment. During pregnancy, the mother only ate sweet potatoes and had never done any antenatal care at the health center and/or hospital. The labor occurred spontaneously at home, assisted by non-medically trained family members, and had his umbilical cord cut with razor. Patients had exclusive breastfeeding until the age of 6 mo, then introduced with sweet potatoes for complimentary feeding from 6 mo old until now. For the past month, he preferred more breast milk and was unwilling to eat solid food.

Parents can sometimes provide formula milk, but due to economic problems, it was often unavailable. During his present illness, the patient can only consume about 50 mL of formula milk or about 50 g of sweet potatoes. Patient had never been immunized, particularly BCG. The history of growth and development is not clear. Patient took several steps and say a few words besides mama, papa at the age of 1 y, and more fluently at 2 y.o.

Upon admission at the ER, the patient was found to be somnolent, looked severely ill, with pulse rate 136 beats/min, respiration rate (RR) 64 breaths/min, axillary temperature (t) 37,6°C, peripheral capillary oxygen saturation (SpO<sub>2</sub>) 93% at room air. His anthropometric measurement upon admission as follow: weight 8 kg, height 86 cm, and head circumference 48 cm, with mid-upper arm circumference (MUAC) 10.5 cm. He had sunken eyes, anemic conjunctivae, but no icteric sclerae. He had dry oral mucosa, with no thrush or redness. He had no enlarged lymph nodes nor abscesses on his neck. On chest examination, we found intercostal, subcostal retraction, with bilateral rhonchi on both lung fields, with no wheezing noted. He had flat and supple stomach, with normal bowel sounds, slow returning turgor, without hepatosplenomegaly. He also had baggy pants with cold extremities and capillary refill time of 2 sec.

The laboratory test results upon admission were hemoglobin of 9.4 g/dL, leukocytes of 7,500  $\mu$ L, platelets of 169,000 $\mu$ L, lymphocytes 22.1%, granulocytes 68.0%, MCV 68.4 fL, MCH 24.9 pg, MCHC 36.4 g/dL, non-reactive anti-HIV, GDS of 45 mg/dL. There was no x-ray examination performed due to unavailability of the service in our institution.

Patient was initially diagnosed as severely wasted, short stature, hypoglycemia, severe dehydration, persistent diarrhea probably bacterial, and community pneumonia.

The patient were then hooked to O<sub>2</sub> at 2 LPM by nasal cannula, given of D10% 40 mL (5 mL/kg) intravenous bolus to treat hypoglycemia, and administered ringer lactate 80 mL/hour (10 mL/kg/h) for 2 h then slowly reduced within 6 h to his maintenance rate using D5 ½ NS. To treat the infection, the patient received ampicillin 250 mg/6 h (125 mg/kg /day) IV, and gentamicin 40 mg/24 h (5 mg/kg/day) IV. We started the enteral diet immediately after resuscitation via the nasogastric tube using the F-100 from the hospital kitchen. Administration of F-100 started with 50 mL (his normally tolerated volume of milk) which was then increased gradually every 4-6 h to reach 60% of the calorie requirement per day. Apart from F-100, we also provided zinc supplementation and vitamin A through the nasogastric tube.

The patients' weight gain was only 300 g over 13 d of admission, even after proper nutritional management. We considered an ongoing untreated TB infection, hence the tuberculin test which shown no induration after 48 h. Nevertheless, we decided to start oral anti-tuberculosis drugs (OAT). After the initiation of OAT, he had weight gain of 100 g/d for the next 13 d and was able to achieve full oral intake by the 23<sup>rd</sup> hospital day. The patient was then discharged after undergoing treatment for 26 d with weight of 9.5 kg and height of 86 cm.

## **DISCUSSION**

Nutrition for infants, children, and adolescents should maintain current weight and support normal growth and development. Dietary intake should provide energy requirements as well as the essential macronutrient and micronutrient needed in sustaining the function of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, affect neurodevelopment, and increase

morbidity and mortality. Worldwide, malnutrition and undernutrition are the leading causes of acquired immunodeficiency, and a major factor underlying morbidity and mortality in children <5 y.o.<sup>13</sup> Immediate determinants of nutritional status are maternal age, occupation and educational status, number of family members, family income, psychosocial factors in the mother-child interactions, childcare practices, child dietary intake and health status, access to clean water and sanitation.<sup>14,15</sup> Malnutrition among children 6-59 mo is influenced more by external factors such as dietary intake and immunity to infection.<sup>3</sup>

In this case, the patient had persistent diarrhea for the past 3 wk and a medical history of community-acquired-pneumonia a year prior. The patient was exclusively breastfed for 6 mo and was further weaned with sweet potatoes from 6 mo old until now. Since the last one month, the patient preferred breast milk compared to solid food, formula milk was often unavailable. The patient was only given sweet potatoes daily, a source of carbohydrates without any protein, fat, and other micronutrients. This showed continuously insufficient food intake and repeated suffered infectious disease.<sup>16</sup> When a child's intake is insufficient to meet his daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life, called reductive adaptation. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs, and reducing inflammatory and immune responses.<sup>7,13</sup>

This patient was a 35-mo.o. boy weighing 8 kg, with height of 86 cm, MUAC 10.5 cm. Based on the WHO classification in this patient weight-for-height Z score was at  $Z < -3SD$ , height-for-age was  $-3 < Z < -2$ , weight-for-age  $Z < -3SD$ , so that this patient diagnosed with

severely wasted, severely underweight, and short stature. The complications were severe dehydration, hypoglycemia, and acute pneumonia, made us take the decision the patient to be hospitalized. Based on the Indonesian guidelines for the prevention and management of severely wasted for under-five children, hospitalization for severely wasted 6-59 mo children with complications and/or comorbidities that lead to malnutrition, such as TB and HIV, poor appetite, and inability of the family to give proper care.<sup>3</sup>

Children with undernutrition are at increased risk of death from infectious diseases and, conversely, severe infectious diseases in early childhood can affect nutritional status.<sup>8</sup> The main effects observed in severe acute malnutrition occur in the T-lymphocytes and the complement system. The number of lymphocytes originating in the thymus gland drastically decreases and the gland atrophies.<sup>16</sup> Lower serum leptin levels in malnutrition children lead to atrophy of thymus cells, lymph nodes, and tonsils leading to impaired cellular immunity. There are reduced differentiation of CD4 cells with normal CD8-T lymphocytes as well as loss of delayed hypersensitivity, impaired phagocytosis and reduced secretory IgA susceptibility to invasive gastrointestinal infection.<sup>17-19</sup> The resultant changes lead to increased susceptibility to infections and severe complications.<sup>16</sup> Repeated exposure to pathogens leads to colonization of bacteria in the intestine with accumulation of inflammatory cells in the small intestinal mucosa, damages the intestinal villi and leads to malabsorption of nutrients which ultimately leads to malnutrition.<sup>19,20</sup> The systemic circulating leptin deficiency in malnutrition is also correlated with several other bacterial, viral and parasitic infections such as TB, pneumonia, sepsis, amoebiasis, malaria and other infection due to defective cytokine production.<sup>18</sup>

Children with fast breathing and/or chest indrawing are classified as having pneumonia.<sup>21</sup> The most commonly isolated organisms in severely malnourished children with pneumonia were *Klebsiella* species, *Staphylococcus aureus*, *Streptococcus pneumoniae* (Pneumococcus), *Escherichia coli*, *Haemophilus influenzae*, and *Salmonella* species. Impaired of immune function, including lower leptin levels cause poorer clearance of *S. aureus* from the lungs increases the spread of this pathogen to the lower respiratory tract.<sup>19,20,22</sup> Arpitha *et al.*<sup>23</sup> reported, severity of malnutrition was a significant risk factor for increased severity of pneumonia. Artawan<sup>24</sup> concluded that nutritional status was related to severity of pneumonia in children. Diagnosis of pneumonia optimally includes a combination of history, clinical signs, and chest X-ray. Adequate laboratory and radiological services are frequently absent in primary healthcare facilities, hence WHO recommends basing the diagnosis of pneumonia primarily on visible clinical parameters, including respiratory rate and chest indrawing.<sup>22</sup> Among well-nourished children, most of the clinical signs have acceptable sensitivity and specificity. In contrast, among children with severe acute malnutrition (SAM), the predictive power of most clinical signs is lower. When fast breathing and lower chest wall indrawing are caused by pneumonia, they persist even after full rehydration, thus allowing for diagnosis of pneumonia after full rehydration.<sup>22</sup>

Based on WHO recommendations, under-five severe malnutrition with complications (hypoglycemia, hypothermia, decreased consciousness/lethargy, or looking sick) need to receive parenteral antibiotics (IM/IV). The selection of ampicillin and gentamicin has considered the coverage of the cause of infection among malnutrition accompanied by complications, both pneumonia and persistent diarrhea.<sup>3</sup>

We monitored our therapy by weighing and recording body weight after the transition phase in g/kg BW/d. The increase in body weight on the 13<sup>th</sup> d of treatment when compared to when it was admitted was still less than 5 g/kg BW/d. Evaluation of patients to find out the root of the problem of insufficient weight gain includes giving F-100 in the form of correct administration, correct frequency and correct volume spent by the patient, and there are comorbidities that have not been resolved.

Tuberculin test on day 13<sup>th</sup> showed no induration after 48 h. The sensitivity of the tuberculin test decreases in severe malnutrition children, and increasing the dose is necessary to increase the sensitivity,<sup>25</sup> so that in these patients the tuberculin dose is increased to 0.1 mL, but still no induration produced. Kumbhojkar *et al.*<sup>26</sup> reported that more than 70% of malnourished children with tuberculin showed negative results, and more positive results in well-nourished children.

Tuberculosis can mimic many common childhood diseases, including pneumonia, generalized bacterial and viral infections, malnutrition, and HIV infection.<sup>27</sup> Undernutrition increases the risk of TB and TB can cause or worsen undernutrition.<sup>8</sup> This is why clinicians in such places rely mostly on a combination of epidemiology, history of exposure, clinical features, chest X-rays, and tuberculin skin test (TST) following WHO criteria in making a diagnosis and treating childhood TB. The Xpert MTB/RIF assay, a highly sensitive real-time polymerase chain reaction (RT-PCR) test, is specific for TB. However, it requires high-quality samples, is expensive, and is not readily available in resource-poor and TB-endemic.<sup>12</sup> National guidelines for the management of TB on children in limited resource area in Bangladesh use symptom-based screening as a good tool in case detection in resource-limited area.<sup>28</sup>

The 1999 WHO manual on the management of severe malnutrition suggested a screening of TB contacts as part of the initial history among children with malnutrition.<sup>8</sup> Routine TB risk assessment among acutely malnourished children, combined with improved linkages with TB services, would help increase TB case finding and improve outcomes for children with TB and undernutrition. Guidelines from South Africa recommended considering TB on children with moderate acute malnutrition (MAM) and SAM, whereas Bangladesh recommended TB screening in the context of specific signs or symptoms such as cough for >2 wk, chest infection that fails to respond to antibiotics, or history of contact with a TB case, which could already count as TB risk assessment.

The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations.<sup>26</sup> Clinical signs of TB in children are largely non-specific, such as unexplained weight loss or failure to grow normally, chronic cough, unexplained fever, especially when it continues for more than 2 wk.<sup>11</sup> Systemic signs and symptoms may appear early or late in the disease course. Daily fever, intermittent or persistent throughout the day, and usually lasts more than one week. The cough is usually unremitting for > 2 wk. Night sweats are uncommon, subjective and nonspecific, and are significant only when they drench the child's clothes and bedding. Chills and rigors are rare, except in disseminated disease. Anorexia and associated wasting or failure to thrive during the past 3–6 mo or having lost >10% of body weight over any interval of time.<sup>27</sup>

Peripheral lymphadenopathy from TB typically consists of a unilateral, enlarged, non-painful, rubbery lymph node, sometimes becoming fluctuant, with or without spontaneous drainage in

the form of a sinus tract. Respiratory signs and symptoms depend on the site, and degree of involvement.<sup>27</sup> The diagnosis of TB can be made with confidence in most children using careful clinical assessment.<sup>28</sup>

Global laboratory initiative (GLI) model TB diagnostic algorithms 2018 recommend if no MTB detected by Xpert MTB/RIF or no test available is the evaluation of the clinical response after 3–5 d of antibiotic treatment. The presumptive TB treatment should start among patient with serious illness, danger signs, worsening conditions, or minimal improvement.<sup>29</sup> However, clinical signs of TB on our patient with severe malnutrition was subtle, and the diagnosis of TB were even more difficult due to the presentation of acute pneumonia, negative TST and unavailability of radiological examination in our institution. After the initiation of antituberculosis, the patient showed weight gain of 10 g/kg BW/d for the next 13 d. Patients were also able to tolerate full oral intake by the 23<sup>rd</sup> d of treatment. The patient was then discharged after 26 d of treatment with no medical complications, good appetite, and good clinical condition. The patient was routinely followed up to pediatric outpatient in our institution for continuous monitoring of weight gain and TB treatment.

The WHO recommends the use of standard-dose combination anti-TB therapy that includes rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) in all children.<sup>30</sup> Children with malnutrition have altered drug metabolism, however, based on a systematic review of the efficacy, safety, and pharmacokinetics of antibiotics in children with SAM, further research is needed to guide optimal antibiotic treatment for these children.<sup>8</sup> There was no significant difference in the half-life of H among the underweight compared to the well-nourished control children.<sup>31</sup>

Roy *et al.*<sup>32</sup> reported no significant difference in the serum concentrations of H in moderately malnourished and well-nourished children. Among children treated for TB with thrice-weekly Z or E, the maximum concentration for Z was significantly reduced in severely malnourished compared with their well-nourished counterparts.<sup>33</sup> However, the maximum concentration for ethambutol showed no significant difference when compared for both groups of children.<sup>30</sup> Malnutrition was not associated with low plasma concentrations of isoniazid, rifampicin and ethambutol.<sup>34</sup> It may be safe to use doses lower than the WHO recommended doses of H, R and Z for acutely malnourished children with TB. However, doses should be increased gradually following nutritional recovery, according to the change in BMI, or weight-for-age and weight-for-height z-scores.<sup>30</sup>

## CONCLUSION

This case report describes the challenge of diagnosing TB in children with severely wasted in limited resource areas. The reduced immune responses due to severely wasted caused subtle clinical signs of TB and decreased sensitivity to tuberculin testing. The unavailability of radiologic examination added further problem in diagnosis. The diagnosis of TB should be considered among children in areas with a high prevalence of TB presenting with severely wasted refractory to proper nutritional management.

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