

Management of Multidrug Resistant Tuberculosis in Paediatrics

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Abstract

Tuberculosis in pediatric patients is estimated to reach 10-15% of the total tuberculosis patient. The highest case of pediatric tuberculosis is found at several low-income countries. MDR-TB cases in pediatrics are often primary MDR-TB, transmitted from infected adults. Pulmonary tuberculosis in pediatric tends to be paucibacillary, which is difficult to diagnose due to unspecific clinical symptoms. *M. tb* culture from the sputum might be negative in 50% of children with active pulmonary TB. Problems related to diagnosis of pulmonary TB in pediatric patients include little amount of bacteria, difficulties in retrieving representative sputum, and higher extrapulmonary cases, especially in children under five years old. The strategy to combat MDR-TB consists of three treatment approaches, namely: standard guideline, empirical guideline, and individual guideline based on each patient.

Guideline recommendation for MDR-TB treatment in pediatric patients are: administer a combination of three effective drugs with special consideration for low number of bacteria and risk of drug resistance, use the drug sensitivity test pattern for adult patient if the drug sensitivity test pattern for pediatric patient is not available, treatments based on the adult drug sensitivity test index can be effective in pediatrics, injection drugs and fluoroquinolones are still considered the main drug for pediatric MDR-TB treatment, and add one or two drugs in the four drug groups (Eto and Cs) while paying close attention to other drugs and cross-resistance. Close monitoring of pediatric MDR-TB patient includes monitoring of clinical symptoms, chest radiograph, *M. tb* culture, AFB sputum, and routine blood examination.

Keywords: MDR- TB in Pediatrics; Diagnosis; Treatment

Introduction

The World Health Organization (WHO) estimated 12 million of people in the world have been infected with tuberculosis, with approximately 650,000 cases of multidrug-resistant tuberculosis (MDR-TB). Tuberculosis in pediatric patients is estimated to reach 10 - 15% of the total tuberculosis patient. The highest case of pediatric tuberculosis is found at several low-income countries. The incidence of MDR-TB has a rapid threefold increase in several areas, for instance from 2.3% to 7.3% in Western Cape, South Africa within the last 15 years. MDR-TB cases in pediatrics are often undiagnosed [1]. Limited data on pediatric MDR-TB showed that the culture of *Mycobacterium tuberculosis* (*M. tb*) and drug sensitivity test are rarely performed due to lack of representative specimen and little amount of *M. tb* bacteria retrieved [2]. Sputum examination and *M. tb* bacteria culture are recommended to follow up the treatment response [1,3]. Moxifloxacin, a substance with a bactericide activity to *M. tb*, is used in the treatment of MDR-TB or patient with anti-tuberculosis drug intolerance [5]. Linezolid can also be used in MDR-TB treatment but its efficacy remains unclear [6]. This literature review discussed the treatment of MDR-TB in pediatrics.

Definition

Multidrug resistant tuberculosis is an *M. tb* bacterial infection resistant to rifampicin and isoniazid with or without resistance to other anti-tuberculosis drug. *Mycobacterium tuberculosis* is considered resistance if 1% or more bacteria in a population are resistant to the drug in recommended dose.

Anti-tuberculosis drug resistance is generally classified into [7,8]:

1. Primary resistance: a resistance case in a patient who has not received any anti-tuberculosis drug or has received anti-tuberculosis for less than one month.
2. Initial resistance: a resistance case in a patient with history of previous uncertain anti-tuberculosis treatment.
3. Secondary resistance: a resistance case in a patient who has received anti-tuberculosis drug for a minimum of 1 month.

M. tb resistance to anti-tuberculosis drug is specifically classified into five categories [6]:

1. Mono-resistance: a resistance to one of the anti-tuberculosis drug.
2. Poly-resistance: a resistance to more than one anti-tuberculosis drug other than the combination of isoniazid dan rifampicin.
3. Multidrug-resistance (MDR): a resistance to at least isoniazid and rifampicin.
4. Extensive drug-resistance (XDR): an MDR-TB with resistance to one of the fluoroquinolone groups and at least one of the second line of anti-tuberculosis injection (capreomycin, kanamycin, and amikacin).
5. Total Drug Resistance (TDR): a resistant to both first and second line anti-tuberculosis treatment. There is no drug available that can be used in this condition.

Rifampicin and isoniazid are the two essential drugs in the treatment of TB in the Directly Observed Treatment Short-course (DOTS) strategy. If isoniazid and rifampicin are no longer sensitive, the number of recovery will be decrease, the length of treatment will be twice longer, and the possibility of drug toxicity will increase.

Epidemiology

The WHO estimated that there are 650,000 cases of MDR-TB in the world in 2012; 3.7% of which originated from the group with previous TB treatment. The WHO also reported that in 2012, the number of TB patients in Indonesia was the 4th highest in the world with an estimation of 450,000 new TB cases each year. According to the 2013 WHO report, there are 622 suspected MDR-TB cases (41 new cases, 557 recurrent TB cases) in Indonesia in 2012. Approximately 1.4% of new TB cases in Indonesia are MDR-TB cases, whereas 29% of the recurrent TB cases are MDR-TB. Indonesia ranks 9 out of 27 countries with the highest MDR-TB burden in the world (WHO, 2012) [9].

The pattern of MDR-TB cases in Persahabatan General Hospital in 1995-1997 consists of 4.6-5.8% primary resistance and 22.9 - 26.07% secondary resistance. Sutoyo., *et al.* studied 3727 patients in Persahabatan General Hospital respiratory outpatient clinic and discovered that 544 patients are diagnosed with MDR-TB within 2005 - 2007 with a frequency of 14.87%. The most prevalent cases were secondary resistance which makes up for 77.2% of cases, followed by primary resistance, which makes up for 22.8% of cases [10,11].

Data on pediatric MDR-TB prevalence remains limited. In Cape Town South Africa, the prevalence of MDR-TB among pediatric patients was 6.7% in 2005 - 2007, higher than that of the previous decade, which was 2.3%. A study by Fairlie., *et al.* showed that the prevalence of MDR-TB among 148 pulmonary tuberculosis pediatric patients in Cape Town was 8.8% [12]. It is difficult to determine the prevalence of MDR-TB in pediatric patients, since the *M. tb* culture and drug sensitivity test are not routinely performed in high prevalence area. This data displays the trend towards increasing prevalence of MDR-TB in pediatric patients [13].

The increase in morbidity and mortality of MDR-TB cases is suspected to be caused by patient factors such as treatment incompliance, lack of information, financial or transportation issues, etc.; as well as health care provider factors, such as inadequate treatment guideline, addition of one drug to the failed guideline, treatment that is not based on sensitivity test, absence of monitoring; and health care system factors, which include drug unavailability, poor drug quality and storage, weak organization, insufficient funding, absence of treatment guideline, and limited microbiology laboratory facilities. Therefore, it can be concluded that MDR-TB has become a man-made phenomenon due to poor health care service and system [7].

Multidrug Resistant Tuberculosis Treatment (MDR-TB)

The consideration for the treatment of drug resistant tuberculosis varies based on the available resources. High-income countries are urged to utilize individual treatment regimens according to the patient needs; whereas low-income countries with limited resources should implement the standard treatment guideline with second-line drugs [14]. The strategy to combat MDR-TB consists of three treatment approaches, namely: standard guideline, empirical guideline, and individual guideline based on each patient. The definitions of each guidelines are as follows [13]:

- 1. Standard guideline:** a guideline designed based on the drugs resistance survey (DRS), which represents the special treatment due to the unavailability of individual sensitivity test. Suspected MDR-TB must be confirmed through drug sensitivity test, if possible. All patients will receive the standard regiment of: **6 Z-(E)-Km-Lfx-Eto-Cs/18 Z-(E)-Lfx-Eto-Cs**
(Z: Pyrazinamide, E: Ethambutol, Km: Kanamycin, Lfx: Levofloxacin, Eto: Ethionamide, Cs: Cycloserine.) Ethambutol should not be given if resistance is proven.
- 2. Empirical guideline:** an individually-modified guideline based on previous anti-tuberculosis treatment and DRS survey data. This empirical guideline is often modified after the result of drug sensitivity test.
- 3. Individual guideline:** a guideline modified based on previous history of anti-tuberculosis treatment and specific patient's drug sensitivity test result.

The treatment of MDR-TB patient is more difficult and longer which in a certain condition may reach up to 24 months with low rate of success. The drugs being used are more expensive and have lower antibacterial activities compared to rifampicin and isoniazid. The main criteria of anti-tuberculosis drugs for MDR-TB based on pharmacology data is divided into three groups of anti-tuberculosis drugs, namely: drugs with bactericide properties (aminoglycoside, ethionamide, and pyrazinamide which work on acid pH), drugs with low bactericide properties (fluoroquinolones), and drugs with bacteriostatic properties (ethambutol, cycloserine, and PAS). Failure to treat MDR-TB patients causes the resistant bacteria to spread to people close to the patient, which in turn leads to the risk of primary resistance or infection of resistant bacteria.

The current standard MDR-TB treatment regimens in Indonesia is the combination of pyrazinamide, ethambutol, kanamycin, levofloxacin, ethionamide, and cycloserine for 6 months, followed with pyrazinamide, ethambutol, levofloxacin, ethionamide, and cycloserine. The recommended injection drugs or intensive phase is based on the conversion of *M. tb* culture. Injection regimens are continued for at least 6 months and a minimum of 4 months after the result of sputum culture or the first *M. tb* culture becomes negative. Individual approach includes results of culture, Acid-Fast Bacilli (AFB) sputum test, chest radiograph, and patient's clinical condition may also help the clinician to determine the discontinuation of injection drugs. The treatment for MDR-TB is recommended to be continued for a minimum of 18 months after the conversion of *M. tb* bacteria culture. There is no data that supports the reduction of treatment period. Treatment of more than 24 months may be performed in a chronic case with extensive lung damage. The strategy for MDR-TB treatment should be established according to the sensitivity test data and the frequency of anti-tuberculosis drug usage in the country. Correct administration of anti-tuberculosis drug and good supervision are essential to prevent and overcome the multidrug resistant TB problem. DOTS concept is also one important measures in ensuring patient compliance and in resolving tuberculosis, especially multidrug resistant tuberculosis [7].

Multidrug Resistant Tuberculosis (MDR-TB) in Pediatric Patients

MDR-TB cases in pediatrics are often primary MDR-TB, transmitted from infected adults. Pulmonary tuberculosis in pediatric tends to be paucibacillary, which is difficult to diagnose due to unspecific clinical symptoms. *M. tb* culture from the sputum might be negative in 50% of children with active pulmonary TB. Problems related to diagnosis of pulmonary TB in pediatric patients include little amount of bacteria, difficulties in retrieving representative sputum, and higher extrapulmonary cases, especially in children under five years old. The consideration of MDR-TB diagnosis is based on bacteriology, as assessed through culture and drug sensitivity test. Chest radiograph and CT-scan may help the diagnosis process. It is therefore important that history of close contact with positive AFB or MDR-TB pulmonary adult patient should be established. Gen Xpert examination can also be used to establish the MDR-TB diagnosis [15].

A cross sectional study by Shah, *et al.* in Mumbai India was conducted to understand the clinical profile of MDR-TB pediatric patients. Patients were divided into monoresistance TB, polyresistance TB, multidrug resistance TB, and extensive drug resistance (XDR-TB). The author used the definition of pre-XDR-TB if the *in vitro M. tb* bacteria culture is resistant to rifampicin, isoniazid, and fluoroquinolones or to one of the aminoglycosides. The analysis of 500 pediatric patients found that 34 (6.8%) of children were resistant to anti-tuberculosis drugs with a prevalence of 6.8%. The average age was 6.8 ± 3.2 years old with the male to female ratio of 13:21. Eighteen pediatric patients (52%) had a history of previous anti-tuberculosis treatment (one patient dropped out of treatment), seven patients had contact history with adult MDR-TB patient and three (10.3%) children was infected with HIV. History of previous TB diagnosis was found in 3 (16.7%) patients with abdominal TB, 12 (66.7%) patients with pulmonary TB, and 1 patient each (5.6%) for lymphadenopathy TB, osteomyelitis TB, and latent TB. According to the anti-tuberculosis drug resistance pattern, there were 14 (41.2%) MDR-TB patients, 11 (32.4%) pre-XDR-TB patients, and 1 patient each (2.9%) for polyresistance TB and XDR-TB. Weight loss was found on 18 (85.7%) female patients compared to 6 (46.2%) male patients ($p=0.019$). Current TB diagnosis was not different between male and female patients [16].

Guideline recommendation for MDR-TB treatment in pediatric patients are as follows [2,15]:

1. Administer a combination of three effective drugs, with special consideration for low number of bacteria and risk of drug resistance.
2. Use the drug sensitivity test pattern for adult patient if the drug sensitivity test pattern for pediatric patient is not available. Treatments based on the adult drug sensitivity test index can be effective in pediatrics.
3. Injection drugs and fluoroquinolones are still considered the main drug for pediatric MDR-TB treatment.
4. Add one or two drugs in the four drug groups (Eto and Cs) while paying close attention to other drugs and cross-resistance.
5. Treatment is administered 6 days every week for 12 - 18 months. The length of treatment in pediatric patient is currently undecided. The length of treatment of MDR-TB in pediatrics with cavity or severe extrapulmonary TB may refer to the length of treatment in adults.

Anti-tuberculosis Drugs	Daily Dose mg/kg BW	Administration	Maximum Dose
Streptomycin	20 - 40	Once daily	1 gram
Kanamycin	15 - 30	Once daily	1 gram
Amikacin	15 - 22.5	Once daily	1 gram
Capreomycin	15 - 30	Once daily	1 gram
Ofloxacin	15 - 20	Twice daily	800 mg
Levofloxacin	7.5 - 10	Once daily	750 mg - 1 gram
Moxifloxacin	7.5 - 10	Once daily	400-800 mg
Ethionamide	15 - 20	Twice daily	1 gram
Prothionamide	15 - 20	Twice daily	1 gram
Cycloserine	15 - 20	Once or twice daily	1 gram
P-salicylic amino acid	150	Twice or thrice daily	12 grams

Table 1: List of anti-tuberculosis drugs for MDR-TB in pediatrics. Cited from [17].

Research on the efficacy of preventive treatment for children with a history of MDR-TB contact is limited. Prospective cohort study by Seddon, *et al.* was conducted to identify the efficacy of preventive treatment for pediatrics with MDR-TB contact history in Western Cape, South Africa. There were 186 pediatric patients enrolled as the study sample with a median age of 34 months (interquartile of 14 - 47 months). The patients were given standard preventive therapy which consisted of ofloxacin (15 - 20 mg/kg BW), ethambutol (20 - 25 mg/kg BW) and isoniazid (15 - 20 mg/kg BW) every day for 6 months. Clinical and radiological evaluation was performed on the 2nd, 4th, 6th, and 12th months. Poor outcome was defined as the occurrence TB case or all-cause mortality. HIV examination was conducted on 17 pediatric patients in which 9 (5%) of them were HIV positive. Treatment compliance was categorized good for 141 (75.8%) patients. Only 7 (3.7%) patients experienced third-degree side effects. One (0.5%) patient passed away and 6 (3.2%) were diagnosed with TB. Factors influencing the poor outcome were < 1 year of age, positive HIV status, exposure to several MDR-TB patients, and low compliance to preventive treatment [17].

Fluoroquinolones are not recommended for younger age pediatric patients due to the risk of arthropathy in animal trial; thus, it must only be given after a clear informed consent to the patient's parents. Every parents or caregivers must report every signs and symptoms of toxicity such as pain on the extremities, swelling, and limited joint movement. Injection drugs must be given in the treatment of pediatric MDR-TB just like the MDR-TB treatment in the adults. Pediatric patients who received aminoglycoside and capreomycin must be followed up for hearing, vestibular, and kidney function. Close monitoring of pediatric MDR-TB patient includes monitoring of clinical symptoms, chest radiograph, *M. tb* culture, AFB sputum, and routine blood examination, if needed. Monthly examination during the intensive phase is recommended to identify side effects, to record the patient's weight, and to have parental consultation regarding the risk of adverse effects and the importance of treatment compliance. Anti-tuberculosis drugs must be adjusted to the patient's weight. Treatment regimens in pediatrics can be adjusted in the event of an adverse effect, although it is less often compared to adults [18].

Conclusion

Guideline recommendation for MDR-TB treatment in pediatric patients are : administer a combination of three effective drugs with special consideration for low number of bacteria and risk of drug resistance, use the drug sensitivity test pattern for adult patient if the drug sensitivity test pattern for pediatric patient is not available, treatments based on the adult drug sensitivity test index can be effective in pediatrics, injection drugs and fluoroquinolones are still considered the main drug for pediatric MDR-TB treatment, and add one or two drugs in the four drug groups (Eto and Cs) while paying close attention to other drugs and cross-resistance. Close monitoring of pediatric MDR-TB patient includes monitoring of clinical symptoms, chest radiograph, *M. tb* culture, AFB sputum, and routine blood examination.

Bibliography

1. Ettehad D., *et al.* "Treatment outcomes for children with multidrug-resistant tuberculosis: a systemic review and metaanalysis". *Lancet* 12.6 (2012): 449-456.
2. Schaaf HS and Marais BJ. "Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians". *Paediatric Respiratory Reviews* 12.1 (2011): 31-38.
3. Soepandi PZ. "Diagnosis and management of MDR- TB". *CDK* 180 (2010): 497-501.
4. Akkerman OW, *et al.* "Drug concentration in lung tissue in multidrug-resistant tuberculosis". *European Respiratory Journal* 42.6 (2013): 1750-1752.
5. Pranger AD., *et al.* "Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience". *European Respiratory Journal* 38.4 (2011): 888-894.
6. Bolhuis MS., *et al.* "Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients". *European Respiratory Journal* 42.6 (2013): 1614-1621.

7. Aditama TY. "MOTT and MDR". *Jurnal Respirologi Indonesia* 24 (2004): 157-159.
8. Isbaniyah F, *et al.* "Tuberkulosis: diagnosis and management guidelines in Indonesia". In: Isbaniyah F, Thabrani Z, Soepandi PZ, Burhan E, Yunus F, Sembiring H, editors. Jakarta: PDPI (2011): 20-50.
9. MDR-Tb. World Health Organization. October 2013 update.
10. Munir SM, *et al.* "The observasional study of MDR-TB patients in pulmonary policlinic Persahabatan Hospital Jakarta Indonesia". *Jurnal Respirologi Indonesia* 30.2 (2010): 72-74.
11. Aditama TY and Soepnadi PZ. "Tuberculosis, treatment and its problem". Third Edition (2000): 31-47.
12. Fairlie L, *et al.* "High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study". *BMC Infectious Diseases* 11 (2011): 28.
13. Nawas A. "Management of MDR-TB dan DOTS plus strategy". *Journal Tuberculosis Indonesia* (2010): 71-77.
14. Caminero JA. "Management of multidrug-resistant tuberculosis and patients in retreatment". *European Respiratory Journal* 25.5 (2005): 928-936.
15. Monedero I and Cesari G. "Management of drug-resistant tuberculosis in special situations". In Caminero JA, editor. Guidelines for clinical and operational management of drug-resistant tuberculosis. Paris: International Union Against Tuberculosis and Lung Disease (2013): 147-173.
16. Shah I and Chilkar S. "Clinical profile of drug resistant tuberculosis in children". *Indian Pediatrics* 49.9 (2012): 741-744.
17. Seddon JAS, *et al.* "Preventive therapy for child contact of multidrug resistant tuberculosis : a prospective cohort study". *Clinical Infectious Diseases* 57.15 (2013): 1677-1684.
18. Francis J. "National Tuberculosis Center and California Department of Health Services. Drug-Resistant Tuberculosis: a survival guide for clinicians". In Loeffler AM, editor. California: California Health and Human Services Agency (2004): 99-127.

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