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Effectivity of Uniform Multidrug Therapy on the Success of Paucibacillary and Multibacillary Leprosy Treatment

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Abstract

Leprosy is a chronic infectious disease caused by Mycobacterium leprae (M. leprae) that involves the integumentary and peripheral nervous system, causing neuropathy, deformity, and disability. Early detection and appropriate treatment are the ways to break the chain of transmission and prevent disability in leprosy patients. The first line of treatment for leprosy is the standard Multidrug Therapy (MDT) regiment consisting of rifampicin, dapsone, and clofazimine. Standard MDT treatment is given based on the leprosy classification of paucibacillary (PB) and multibacillary (MB). The utilization of the standard MDT regiment has some limitations, particularly where there is a limited supporting test facility, causing difficulty in determining the leprosy classification accurately. An alternative regiment proposed to substitute the standard MDT is the Uniform-MDT (U-MDT). Several studies have been conducted on the use of U-MDT and have produced promising results for the treatment of PB and MB leprosy.

Key words: Leprosy; Multibacillary; Multidrug therapy; Paucibacillary

INTRODUCTION

Leprosy or Morbus Hansen (MH) is a disease that attacks the integumentary system and the peripheral nervous system causing neuropathy, deformity, and disability. The disease is caused by bacteria called *M. leprae* which has a long incubation period (on average ≥ 5 years).[1] The number of active leprosy cases undergoing treatment all over the world until the end of 2020, according to the World Health Organization (WHO), was 129,192 people or 16.6 per one million people.[2] This number has decreased by 27% compared to the previous year, which was thought to be an impact of the Coronavirus Infection Disease-19 (COVID-19) pandemic. The highest number of cases was in South East Asia, which reached 61.1%, and the countries with the highest number of cases were Brazil, India, and Indonesia with a total of 72.5% of cases.[2]

The World Health Organization introduced the leprosy classification system consisting of two categories, the PB and MB. These two categories are based on clinical findings and the bacterial index.[3] The prevalence of MB leprosy all over the world in 2020 was 85,686 cases, out of a total of 129,192 active cases.[2] In Indonesia, the prevalence of leprosy in 2020 was 0.49 cases per 10,000 people, with 86.67% cases being MB leprosy.[4] Early detection of leprosy cases, finding an obscure source of infection, and tracking the rate of transmission in the community are the measures in leprosy control. The indicators used to determine the success of leprosy control are the number of second grade disability, the proportion of MB leprosy, and the proportion of new pediatric leprosy patients (0-14 years old).[1,2,4] In Indonesia, in 2020, the number of people with second grade disability was 2.32 per 100,000 people which tends to decrease each year. However, the proportion of pediatric leprosy patients was 10.08%, which has not changed much from the previous years. This data shows that early detection of leprosy cases and prevention of delayed cases have been successful, however the transmission rate in society is still considerably high.[4]

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Treatment of standard MDT for leprosy by the WHO is based on the classification of PB and MB. The cure rate of patients receiving the MDT regiments reached 99%, and reports of drug resistance were low.[5, 6]A novel innovation for the regiment of leprosy treatment was first discussed in the WHO forum in 2002. The Uniform Multidrug Therapy is a single regiment of rifampicin, dapsone, and clofazimine that was recommended by the WHO in 2018 to be administered with a treatment duration of six months for PB leprosy and 12 months for MB leprosy.[6] The use of U-MDT regiment still raises some controversies. Nevertheless, this approach is thought to support the continuity of the leprosy control program in the future.[7, 8]

LEPROSY CLASSIFICATION ACCORDING TO WORLD HEALTH ORGANIZATION

Leprosy can be classified into two types based on clinical and bacteriological findings, which are the PB and MB types. The WHO first introduced this classification in 1982 with the goal of simplifying the process of diagnosis and treatment in the field, particularly in areas with limited supporting test facilities.[3] Leprosy with five or less skin lesions without evidence of bacillus bacteria from skin smear is categorized as the PB type. If there are six or more skin lesions with evidence of a positive skin smear, the leprosy is categorized as MB type.[9] In India, the National Leprosy Eradication Program (NLEP) modified the WHO classification and added an indicator of peripheral nerve involvement. If there is one or no involvement of the peripheral nerve, it is categorized as PB leprosy, while if there is more than one involvement of the peripheral nerve, it is categorized as MB leprosy.[10]

PATHOGENESIS OF LEPROSY

The process of leprosy transmission is through the respiratory tract. However, transmission from a skin lesion still cannot be excluded. Long term contact with a leprosy patient and a dense population are the main risk factors of transmission. The bacteria then spread systemically via a hematogenous mechanism. The *M. leprae* bacteria tend to prefer tissue with a lower temperature, but they can also be found in the lymph nodes, liver, and bone marrow.[11, 12] *M. leprae* has an affinity for the peripheral nerve cells, particularly the Schwann cells, therefore causing demyelination of nerves, loss of axonal conduction, and producing numbness.[9] The Schwann cells are surrounded by a basal lamina consisting of laminin-2 isoform, heparin sulfate proteoglycan, collagen IV, and nidogen as a receptor of *M. leprae*.[12] If the immunity of the host is in good condition, disease progression can be prevented. It is reported that up to 95% of patients exposed to *M. leprae* do not develop leprosy.[6] The characteristics of susceptible individuals for leprosy disease progression are the innate immunity affected by the PARK2/PCRG gene, immunosuppression conditions including undergoing chemotherapy, transplantation, HIV infection, and the elderly.[9]

Patients with leprosy disease can have a range of spectrums of clinical manifestations. Some patients will develop primary neurological leprosy without skin lesion and some will develop leprosy with various kinds of skin lesion. In the beginning, the skin lesions can be indeterminate, but then they will develop into polar tuberculoid (TT) type, polar lepromatous (LL) type, or between both of them, which is called borderline (BT, BB, or BL).[11] PB leprosy (in a spectrum close to the TT pole) has a good cellular immune response with the presence of Th-1 cytokine, while the MB type (in a spectrum close to the LL pole) shows impaired cellular immune response and high antibody response with the presence of Th-2 cytokine. Both the number of acid-fast bacilli and IgM anti-phenolic glycolipid-I (anti-PGL-I) are low or negative in PB and increased in MB.[11, 13]

A leprosy reaction is an acute exacerbation in the clinical course of leprosy, which is a chronic disease. Leprosy reaction occurs due to the process of immune response between the antigen and the patient's immunity. This reaction may develop before, during, or after leprosy treatment. Leprosy reactions consist of type one reaction (reversal reaction) and type two reaction (erythema nodosum leprosum).[12] Reversal reaction mainly occur in borderline type leprosy, while erythema nodosum leprosum mainly occur in BL and LL type leprosy (Figure 1).[13]

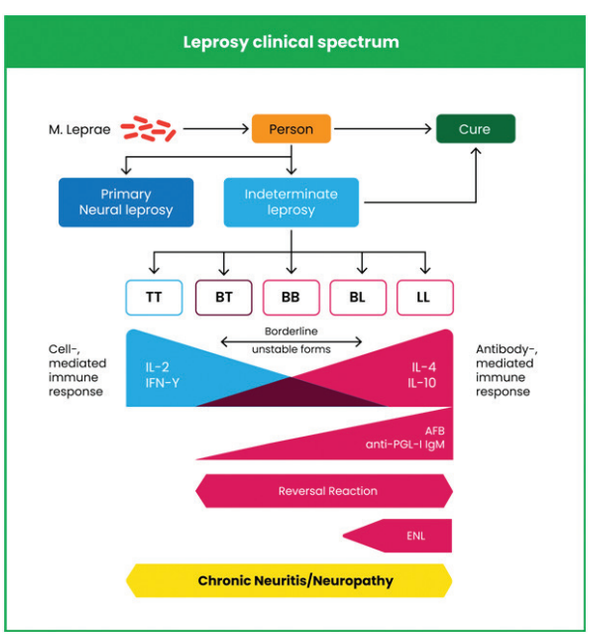

Figure 1. Clinical spectrum of leprosy[13]

STANDARD MDT REGIMENT FOR LEPROSY TREATMENT

Dapsone or diaminodiphenyil sulfone (DDS) is the first drug used as a monotherapy for leprosy treatment in 1941. Dapsone was first synthesized in 1908

in Germany. This drug has a bacteriostatic effect on *M. leprae* and can inhibit folic acid synthesis. The resistance of *M. leprae* to dapsone was first identified in 1960 and it caused the use of dapsone as a monotherapy for leprosy to be abandoned.[12] The use of MDT to replace monotherapy with dapsone for leprosy treatment was first introduced by the WHO in 1982.[9] The benefits of MDT treatment include preventing resistance of *M. leprae* to the drug by reducing ineffectiveness, and reducing the risk of reaction and relapse in patients.[12]

The drugs in the MDT regiment for leprosy treatment according to the WHO guideline consist of rifampicin and dapsone for the PB type, and rifampicin, dapsone, and clofazimine for the MB type. The use of combination of more than one antibiotic was implemented to prevent the development of resistance to a single anti-leprosy drug.[5] The rate of relapse after standard MDT treatment according to the WHO were 0.77% for MB type and 1.07% for PB type at 9 years after treatment completion.[14] The dosage and duration of treatment with MDT regiment is based on the type of leprosy and patient's age (Table 1).[6]

Table 1. WHO Recommendation for the MDT Regiment for Leprosy[6]

Age group	Drug	Dosage and frequency	Duration	
			PB	MB
Adults	Rifampicin	600 mg once per month	6 months	12 months
	Dapsone	100 mg per day		
	Clofazimine	300 mg once per month and 50 mg per day		
Children (10 – 14 years old)	Rifampicin	450 mg once per month	6 months	12 months
	Dapsone	50 mg per day		
	Clofazimine	150 mg once per month and 50 mg every two days		
Children <10 years old or <40 kg	Rifampicin	10 mg/kgBB once per month	6 months	12 months
	Dapsone	2 mg/kgBB per day		
	Clofazimine	100 mg once per month, 50 mg twice per week		

U-MDT REGIMENT FOR LEPROSY TREATMENT

Other than the standard MDT regiment, the WHO have also reviewed the novel regiment of U-MDT for leprosy treatment. Although the standard MDT regiment have been proven to be effective, there are several limitations, including the long treatment duration causing a high drop-out rate, and the risk of misclassification of leprosy type if only based on the number of skin lesions.[15] Based on these consideration, the WHO have developed the U-MDT which consist of a single regiment of rifampicin, dapsone, and clofazimine for 6 months for PB type leprosy and 12 months for MB type leprosy. The dosage given for PB type is similar to the standard MDT for MB type.[6, 7] (Table 1). The World Health Organization have recommended the use of U-MDT for leprosy treatment nationally in a country in 2018.[6]

STUDIES FOR THE EFFECTIVITY OF U-MDT FOR THE TREATMENT OF PB AND MB TYPE LEPROSY

The different use MDT regiment for PB type and MB type leprosy require the ability to classify leprosy accurately. In several conditions, such as where there is limited supporting test facility or the variable spectrum of leprosy causing difficulty in determining the leprosy classification accurately. The development of U-MDT regiment is a strategy to reduce errors in classification of leprosy type.[1, 16] The problem that rise concern from the use of U-MDT is the addition of clofazimine for PB type leprosy, whether or not it will benefit the patients. A study of 48 patients with PB type leprosy in India, compared the administration of U-MDT and the standard MDT PB regiment. The result found superior clinical improvement in patients with PB type leprosy receiving the U-MDT regiment (90.9%) compared to the group receiving MDT PB (27.3%). Improvement of peripheral nerve enlargement in the group receiving U-MDT was 70% and in the MDT PB group was 37.5%, as for the histological resolution, it was 72.8% in the U-MDT group and 54.5% in the MDT PB group.[16]

The World Health Organization supported an international open trial in 2003 which mainly took place in several centers in India and China to further evaluate the risk and benefit of the use of U-MDT regiment for PB and MB type leprosy.[17] The process of subject recruitment took place in 2003 until 2007. A total of 2,912 patients participated in the trial, with 1,777 PB type leprosy patients and 1,135 MB type leprosy patients. All participants received the U-MDT regiment for 6 months, then they were evaluated annually to

assess relapse or other side effect. The study report after the second-year evaluation from initial treatment with U-MDT showed promising results in improvement of clinical status of skin lesion. Evaluation at completion of U-MDT treatment found higher proportion of inactive lesion in the PB type patients compared to MB type patients (27% vs 6%; p<0.001). As for the first-year evaluation after U-MDT treatment completion (59% vs 37%; p<0.001) and second-year evaluation (57% vs 28%; p<0.001). The side effect of clofazimine which was skin pigmentation has been reported, but they were temporary and was within the acceptable limits for the patients.[17, 18]

Another comparative study was also conducted in the same period in India to compare the effectivity of U-MDT and the standard WHO MDT regiment in patients with PB and MB type leprosy.[18, 19] Rao et al., divided the study group that received the U-MDT regiment for six months and the control group received the WHO standard MDT regiment for six months for patients with PB and 12 months for MB patients. Patients with PB type leprosy who received U-MDT and the standard MDT regiment both showed good clinical improvement. However, in the U-MDT regiment group there were more progressive clinical improvement compared to the standard WHO regiment at follow-up after treatment completion at 6 months (61% vs 78%), 18% (94% vs 86%), and 24 months (100% vs 82%). Nevertheless, the differences in progressivity were not statistically significant. Patients with MB type leprosy who received U-MDT regiment were reported to have less favorable clinical improvement, which was 50% at 12 months, 67% at 18 months, and 75% at 24 months after treatment. While the group receiving the standard WHO MDT regiment had good clinical improvement, which was 36% at 12 months, 45% at 18 months, and 77% at 24 months. The differences between the two groups of MB type were statistically significant. Therefore, the use of U-MDT is considered to be effective in PB type leprosy but less effective in MB type patients compared to the 12 months regiment.[18, 19]

A study in China which participated in the international open trial released the results of the study on the conversion of bacterial index (BI) and leprosy reaction in MB type patients treated with the U-MDT regiment. Initial follow-up was until 3 years after treatment completion with U-MDT. The result found significant reduction of BI and 73.5% of patients were declared to be negative BI, 13 patients (14.6%) had leprosy reaction, and one patient had a relapse.[20] Subsequent follow-up was done at 6 years after treatment completion with U-MDT and there were 98.7% of patients with negative BI. The authors concluded that U-MDT can quickly reduce the bacilli activity, reduced the BI permanently, produce low relapse rate, and acceptable rate of leprosy reaction.[21] This study conducted another follow-up at 8 years after treatment completion with U-MDT. The result found negative BI in 100% of the patients, 53% of patients had leprosy reaction, and 1.3% of patients had a relapse. This findings showed the effectivity of U-MDT treatment in MB type patients was still good until the end of 8th year.[18,22] The final results of the open trial conducted in India and China was published in 2016 with good results, the low relapse rate in PB and MB type (relapse risk 0.11% and 0.37%), low rate of side effects (0.79 in PB and 2.64 in MB), treatment compliance was up to 99%, and the pigmentation effect of clofazimine was only temporary and can be tolerated by the patients. Therefore, this study recommended the use of U-MDT regiment in national leprosy program.[7]

A study that compared the use of U-MDT regiment and the standard 12 months MDT MB regiment in patients with MB type leprosy was also conducted in Bangladesh.[23] A total of 1,612 patients with MB type leprosy was divided in to groups receiving U-MDT and the standard MDT MB, then they were followed until 8 years after treatment completion. The result found that there was no significant difference in the relapse rate and BI between those receiving U-MDT and the standard MDT MB. The conclusion of this study was the change in treatment duration from 12 months to 6 months in MB type leprosy did not increase the relapse rate.[23]

A clinical trial was first conducted to determine the efficacy of U-MDT in leprosy patients with randomized controlled trial (RCT) by the leprosy control agency in Brazil.[24] Subjects were divided in to four groups, 2 experiment groups (U-MDT/PB and U-MDT/MB) and 2 control groups (R-MDT/PB and R-MDT/MB). There were a total of 858 subjects who met the inclusion criteria in the study.[24] The result found that there was no statistically significant difference in leprosy reaction rate between the experiment and the control groups. There was also no statistically significant difference in the frequency of first leprosy reaction in the first two years since treatment administration between the groups receiving R-MDT and U-MDT. Moreover, there was no specific leprosy reaction associated with treatment duration.[25] Analysis of the frequency of leprosy reaction in MB patients was not significantly different between those receiving R-MDT and U-MDT. There was no statistically significant difference between the four groups in comparison, U-MDT and R-MDT, with BI lower and higher than three. Analysis of BI reduction was also conducted by estimation of decrease in morphological index (MI) as a function of time. This analysis showed a considerably high reduction in BI in patients with the standard MDT regiment, however this reduction was not significantly higher compared to patients treated with the U-MDT.[26] The final result of an RCT study in Brazil showed the relapse rate was 2.6 cases per 1000 patients per year in patients receiving U-MDT.[24]

A descriptive epidemiological study on U-MDT to identify the satisfaction rate of PB patients regarding the use of clofazimine showed that there was only

6.9% of subjects who wanted to discontinue treatment due to changes in skin pigmentation. The result of this study showed that the use of clofazimine in the treatment of PB patients had no negative impact to patient satisfaction.[27] The four subject groups had similar drug side effects, with the highest frequency found in this study was skin pigmentation and xerosis. Furthermore, there were also hematologic changes with higher risk of anemia in female subjects and MB patients treated with the 12 months MDT. The shorter the treatment duration, the more minimal the side effects will be, therefore U-MDT regiment is declared to be safe and has the potential to be implemented in leprosy control programs.[28]

Table 2. Studies of The Effectivity of U-MDT on The Success of PB and MB Type Leprosy Treatment

Study	Method	Participants	Intervention	Outcome	Results
Prasad, et al. (2005)	*Open comparative study (India)*	44 patients with PB type leprosy	22 patients received U-MDT, 22 patients received standard MDT PB	Clinical and histological improvement	Clinical improvement was significantly superior in patients receiving U-MDT at 6 months after treatment, but not significantly different at 1 year after treatment
Kroger, et al. (2008)	*Open trial (uncontrolled) (India & China)*	2912 subjects (1777 PB type leprosy; 1135 MB type leprosy)	U-MDT for both PB and MB patients	Clinical improvement and follow-up every year until the 2nd year	Proportion of clinical improvement was significantly superior in PB type leprosy at treatment completion, 1 year after treatment and 2 year after treatment. There were 6 patients with confirmed relapse.
Rao, et al. (2009)	*Open comparative study (India)*	64 leprosy patients with 32 PB type (18 study, 14 control) and 32 MB type (10 study, 22 control)	Study group received U-MDT regiment. Control group received standard WHO MDT	Clinical and histopathological improvement, with follow-upevery 6 months for 24 months	In PB type patients: Clinical improvement was superior in study group compared to control group, but not significant. Histopathologically, there were better response in study group compared to control group (number of biopsy was too small for statistical analysis).
Shen, et al. (2015)	*Open trial (uncontrolled) (China)*	114 patients with MB type leprosy (only 75 lasted until the end of study period)	Treatment with U-MDT for 6 months	Assessment of bacterial index, leprosy reaction, and relapse, with follow-up every year until the 6th year	U-MDT was declared effective for patients with MB type leprosy. Negativity rate of the smear was 98.7%. The conversion of BI and frequency of leprosy reaction was similar in patients treated with MDT at 1 and 2 year. Relapse rate was 0.06 per 100 patient-years (one per 1677 patient-years)
Liangbin, et al. (2016)	*Open trial (uncontrolled) (China)*	114 patients with MB type leprosy (only 72 lasted until the end of study period)	Treatment with U-MDT for 6 months	Assessment of bacterial index, leprosy reaction, and relapse, with follow-up every year until the 8th year	Negativity rate of the smear was 100%. Conversion of BI and frequency of leprosy reaction was similar in patients treated with MDT at 1 and 2 year. Relapse rate was 1.3% in 8 years or 0.035 per 100 patient-years (one per 2836 patient-years)
Manickam, et al. (2016)	*Open trial (uncontrolled) (India & China)*	2091 patients with PB type leprosy and 1298 with MB type leprosy	Treatment with U-MDT for 6 months	Assessment of drug side effects, relapse, leprosy reaction, disability, neuritis	Relapse rate was within recommended limits, minimal drug side effects, pigmentation due to clofazimine was acceptable for both patient groups.

Butlin, et al. (2016)	*Open comparative study (Bangladesh)*	918 patients diagnosed with MB type leprosy in 2005 (study group), 694 patients diagnosed with MB type leprosy in 2004 (control group)	Treatment with U-MDT for 6 months for study group, 12 months for control group	Assessment of bacterial index and relapse, with follow-up until the 10th year	The reduction in treatment duration for MB type leprosy to 6 months did not increase relapse rate.
Penna MLF, et al. (2012)	*Open label, randomized controlled trial (included in Randomized Clinical Trial for Uniform Multidrug Therapy for Leprosy Patients in Brazil* (U- MDT/CT-BR))	613 patients with MB type leprosy	323 patients received U-MDT, 290 patients received standard WHO MDT	Assessment of the association between treatment duration and frequency of leprosy reaction	In BI<3, there was a significant difference in leprosy reaction between treatment groups, but there was no difference at 2 years after treatment. There was no specific association between leprosy reaction and treatment duration.
Penna MLF, et al. (2014)	*Open label, randomized controlled trial* (included in U- MDT/CT-BR)	613 patients with MB type leprosy	323 patients received U-MDT, 290 patients received standard WHO MDT	Assessment of the association between treatment duration and reduction of BI	Higher reduction in BI in patients receiving standard MDT, but not significant.
Ferreira, et al. (2014)	*Descriptive cross-sectional epidemiologic study* (included in U- MDT/CT-BR)	A total of 342 subjects with 41 PB type receiving U-MDT, 33 PB type receiving R-MDT, 150 MB type receiving U-MDT, and 118 MB type receiving R-MDT	Interview with predetermined questionnaire	Description of patient profiles and satisfaction regarding U-MDT treatment	Addition of clofazimine in the U-MDT regiment did not cause a reduction in satisfaction of PB type patients.
Penna GO, et al. (2017)	*Open label, randomized controlled trial* (included in U- MDT/CT-BR)	A total of 613 patients with MB type leprosy	323 patients received U-MDT, 290 patients received R-MDT	Frequency of leprosy reaction, reduction of BI, progression of disability and relapse	There was no significant difference in relapse rate, leprosy reaction, reduction in BI, and disability progression between those receiving U-MDT and R-MDT.
Cruz, et al. (2018)	*Open label, randomized controlled trial* (included in U- MDT/CT-BR)	A total of 753 leprosy patients (159 PB type and 594 MB type)	77 PB patients received U-MDT, 82 PB patients received R-MDT, 321 MB patients received U-MDT, 273 MB patients received R-MDT	Comparison of the side effects of U-MDT and R-MDT regiments	In general, there was no significant difference in side effects of U-MDT and R-MDT. The risk of anemia was significantly higher in female patients and MB type patients receiving R-MDT.

The overall results from the studies in Brazil, China, India, and Bangladesh supported the hypothesis that the U-MDT regiment given for six months for both PB and MB type leprosy can be a legitimate option to be implemented in leprosy endemic countries to continue leprosy control programs.[5,29] According to the previously conducted studies, it can be concluded that the use of U-MDT regiment has some benefits, however it also has some limitations for the treatment of leprosy. Several benefits of the U-MDT regiments include the less complicated process in determining treatment regiment, less treatment duration for patients with MB type therefore increasing treatment compliance and reduce risk of drug side effects, less impact of errors in determining leprosy classification (using the U-MDT regiment, patients who were supposed to be classified as MB type but misdiagnosed as PB type will also receive treatment with three type of drugs), and simpler logistics because this regiment will only need two types of blister packages, the adult U-MDT package and pediatric U-MDT package.[6] The limitations of the use of U-MDT are the lack of evidence from studies using RCT design since there has only been one study in Brazil. Previous studies in other countries were mostly open trial studies and there were no control group as a comparison. The guideline for leprosy treatment by the WHO in 2018 stated that the U-MDT regiment has more benefits for the treatment of PB type leprosy. However, the evidence that support the use of U-MDT regiment for six months in patients with MB type leprosy are currently still inadequate and there is a potential of increased risk

of relapse in patients with MB type.[5, 6, 29] Based on these considerations, the WHO recommended the use of U-MDT regiment for PB type leprosy for six months and for MB type leprosy treatment is still given for 12 months.[6] Until today, there has not been a report on the use of U-MDT as part of a national leprosy control program in any country, except as clinical trials or for research purposes.

CONCLUSION

Leprosy is a chronic infectious disease caused by *M. leprae*, characterized by nerve damage, skin lesions, and progressive weakness that affect various parts of the body. Early detection and appropriate treatment are the keys to reducing transmission and preventing disability in patients. Treatment of the standard MDT was based on the classification of PB type and MB type leprosy. An alternative regiment was proposed to replace the standard MDT regiment, which is the U-MDT. The World Health Organization has recommended the use of U-MDT given for six months for PB type leprosy and for duration of 12 months for MB type leprosy as part of a national leprosy control program.

REFERENCES

1. World Health Organization (WHO). Towards zero leprosy: Global Leprosy (Hansen's disease) Strategy 2021-2030. Word Health Organization. New Delhi: World Health Organization; 2021. 1–30 p.
2. World Health Organization (WHO). Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. Wkly Epidemiol Rec. 2020;96(36):421–44.
3. Gaschignard J, Grant AV, Thuc N Van, Orlova M, Cobat A, Huong NT, et al. Pauci- and Multibacillary Leprosy: Two Distinct, Genetically Neglected Diseases. PLoS Negl Trop Dis. 2016;10(5):e0004345. https://doi.org/10.1371/journal.pntd.0004345
4. Kementerian Kesehatan Republik Indonesia. Profil Kesehatan Indonesia 2020. Pusat Data dan Informasi Kemenkes RI. Jakarta: Kementerian Kesehatan RI; 2021.
5. Lockwood DNJ. Treatment of Leprosy. In: Scollard DM, Gillis TP, editors. International Textbook of Leprosy. International Textbook of Leprosy; 2019. p. 1–17.
6. World Health Organization (WHO). Guidelines for the diagnosis, treatment and prevention of leprosy. World Health Organization. New Delhi: World Health Organization; 2018.
7. Manickam P, Mehendale SM, Nagaraju B, Katoch K, Jamesh A, Kutaiyan R, et al. International open trial of uniform multidrug therapy regimen for leprosy patients: Findings & implications for national leprosy programmes. Indian J Med Res. 2016;144:525–35. https://doi.org/10.4103/0971-5916.200888
8. Saunderson PR. Uniform multidrug therapy for leprosy – Time for a rethink? Indian J Med Res 2016;144:499–501. https://doi.org/10.4103/0971-5916.200884
9. Bhandari J, Awais M, Robbins BA, Gupta V. Leprosy [Updated 2021 Nov 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022
10. Kumar B, Uprety S, Dogra S. Clinical Diagnosis of Leprosy. In: Scollard DM, Gillis TP, editors. International Textbook of Leprosy. International Textbook of Leprosy; 2017. p. 1–24.
11. Scollard DM. Pathogenesis and Pathology of Leprosy. In: Scollard DM, Gillis TP, editors. International Textbook of Leprosy. International Textbook of Leprosy; 2016. p. 1–26.
12. Mungroo MR, Khan NA, Siddiqui R. Mycobacterium leprae: Pathogenesis, diagnosis, and treatment options. Microb Pathog. 2020;149:104475. https://doi.org/10.1016/j.micpath.2020.104475
13. Salgado GC, de Brito AC, Salgado UI, Spencer JS. Leprosy. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's Dermatology. 9th ed. New York: McGraw-Hill Education; 2019. p. 2892–924.
14. Maymone MBC, Venkatesh S, Laughter M, Abdat R, Hugh J, Dacso MM, et al. Leprosy: Treatment and management of complications. J Am Acad Dermatol. 2020;83(1):17–30. https://doi.org/10.1016/j.jaad.2019.10.138
15. Goncalves H de S, Pontes MA de A, Bührer-Sékula S, Cruz R, Almeida PC, de Moraes MEA, et al. Brazilian clinical trial of uniform multidrug therapy for leprosy patients - The correlation between clinical disease types and adverse effects. Mem Inst Oswaldo Cruz. 2012;107:74–8. https://doi.org/10.1590/S0074-02762012000900013
16. Prasad PVS, Babu A, Kaviarasan PK, Viswanathan P, Tippoo R. MDT-MB therapy in paucibacillary leprosy: A clinicopathological assessment. Indian J Dermatol Venereol Leprol. 2005;71(4):242–5.https://doi.org/10.4103/0378-6323.16614
17. Kroger A, Pannikar V, Htoon MT, Jamesh A, Katoch K, Krishnamurthy P, et al. International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. Trop Med Int Health. 2008;13(5):594–602. https://doi.org/10.1111/j.1365-3156.2008.02045.x
18. Cruz RC da S, Bührer-Sékula S, Penna MLF, Penna GO, Talhari S. Leprosy: current situation, clinical and laboratory aspects, treatment history and perspective of the uniform multidrug therapy for all patients. An Bras Dermatol. 2017;92(6):761–73. https://doi.org/10.1590/abd1806-4841.20176724
19. Rao PN, Suneetha S, Pratap DVS. Comparative

study of Uniform-MDT and WHO MDT in Pauci and Multi bacillary leprosy patients over 24 months of observation. Lepr Rev. 2009;80(2):143–55.
20. Shen J, Bathyala N, Kroeger A, Arana B, Pannikar V, Mou H, et al. Bacteriological results and leprosy reactions among MB leprosy patients treated with uniform multidrug therapy in China. Lepr Rev 2012;83(2):164–71.
21. Shen J, Yan L, Yu M, Li J, Yu X, Zhang G. Six years' follow-up of multibacillary leprosy patients treated with uniform multi-drug therapy in China. Int J Dermatol. 2015;54(3):315–8. https://doi.org/10.1111/ijd.12573
22. Liangbin Y, Jianping S, Meiwen Y, Guocheng Z, Jinlan L, Xiufeng Y. Results of eight years follow up among multibacillary patients treated with Uniform Multidrug Therapy in China. Lepr Rev. 2016;87(3):314–21.
23. Butlin CR, Pahan D, Maug AKJ, Withington S, Nicholls P, Alam K, et al. Outcome of 6 months MBMDT in MB patients in Bangladesh- preliminary results. Lepr Rev. 2016;87(2):171–82.
24. Penna GO, Pontes MA de A, Cruz R, Gonçalves H de S, Penna MLF, Bührer-Sékula S. A clinical trial for uniform multidrug therapy for leprosy patients in Brazil: Rationale and design. Mem Inst Oswaldo Cruz. 2012;107:22–7. https://doi.org/10.1590/s0074-02762012000900005
25. Penna MLF, Buhrer-Sékula S, Pontes MADA, Cruz R, Gonçalves HDS, Penna GO. Primary results of clinical trial for uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): reactions frequency in multibacillary patients. Lepr Rev. 2012;83(3):308–19.
26. Penna MLF, Bűhrer-Sékula S, Pontes MA raci de A, Cruz R, Gonçalves H de S, Penna GO liveira. Results from the clinical trial of uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): decrease in bacteriological index. Lepr Rev. 2014;85(4):262–6.
27. Ferreira IPS, Buhrer-Sékula S, De Oliveira MR egina F, Gonçalves H de S, Pontes MA raci de A, Penna ML úcia F, et al. Patient profile and treatment satisfaction of Brazilian leprosy patients in a clinical trial of uniform six-month multidrug therapy (U-MDT/CT-BR). Lepr Rev.2014;85(4):267–74.
28. Cruz RC da S, Bührer-Sékula S, Penna GO, de Moraes MEA, Gonçalves H de S, Stefani MM de A, et al. Clinical trial for uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Adverse effects approach. An Bras Dermatol. 2018;93(3):377–84. https://doi.org/10.1590/abd1806-4841.20186709
29. Penna GO, Bührer-Sékula S, Kerr LRS, Stefani MM de A, Rodrigues LC, de Araújo MG, et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients. PLoS Negl Trop Dis. 2017;11(7):1–19. https://doi.org/10.371/journal.pntd.0005725