

Diagnosis and Management of Leprosy

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ABSTRACT

Background: Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, which tends to attack peripheral nerves and skin. The diagnosis of leprosy is based on the presence of one of three cardinal signs. Early diagnosis of leprosy is critical and is made through clinical examination and investigation. **Purpose:** To discuss the diagnosis, laboratory examination, and treatment of leprosy, considering that early diagnosis and appropriate treatment are the key elements in breaking the chain of transmission and preventing leprosy patients' disabilities. **Review:** Leprosy is a chronic granulomatous infectious disease caused by the *Mycobacterium leprae*. Based on clinical appearance, histopathology findings, and immunological, leprosy is grouped into six forms using the Ridley-Jopling classification, namely Tuberculoid (TT), Borderline Tuberculoid (BT), Borderline-borderline Mid-borderline (BB), Borderline-lepromatous (BL), Subpolar Lepromatous (LLs), and Polar Lepromatous (LLp). Based on the treatment category, leprosy is grouped into paucibacillary (PB) and multibacillary (MB). Leprosy is often diagnosed clinically, and skin scraping smear remains the preferred laboratory method. The negative results of smear skin scraping may not necessarily exclude leprosy. Therefore, a higher sensitivity test might be needed to detect *M. leprae*. Treatment with Multi-Drug Therapy (MDT) is adjusted based on the type of leprosy, whether it belongs to the PB or MB group. Treatment of PB type, regimens are rifampicin and dapsone, while in MB type, the patients received rifampicin, dapsone, and clofazimine regimens. **Conclusion:** A proper diagnosis for leprosy, both through physical examination and laboratory examination, is required to determine an effective MDT treatment and break the chain of disease transmission.

Keywords: leprosy, diagnosis, management.

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BACKGROUND

Morbus Hansen, better known as leprosy, is a chronic infectious disease caused by *Mycobacterium leprae*, which tends to attack peripheral nerves and skin. This disease has been known as far back as 3000 years ago, and its estimated origin was Asia or Africa. The term leprosy was coined in an appreciation to a Norwegian doctor, Gerhard Armauer Hansen, who was the first to discover that *Mycobacterium leprae* is the causative bacterium of leprosy.^{1,2}

The World Health Organization (WHO) data of 2017 suggests that Indonesia is one of the top 3 countries with the highest new leprosy cases. India, Brazil, and Indonesia contribute as much as 80.2% of new leprosy cases worldwide. There were 15,910 new cases in Indonesia. During 2015–2017, there were 3,373 new leprosy cases East Java, 1,813 new cases in West

Java, 1,644 in Central Java, and 1,091 in South Sulawesi.³⁻⁵

Leprosy diagnosis is determined as one out of three cardinal signs is present: (i) loss of sure sensation in pale (hypopigmented) or reddish skin; (ii) thickening of peripheral nerve or (iii) the presence of acid-fast bacilli/AFB in the skin scraping. The Multibacillary (MB) leprosy type has a positive AFB test result. Several other tests, including histopathology examination, serology, include PGL-1 antibody titer, and Polymerase Chain Reaction (PCR) examination. A diagnostic examination in the milder form of leprosy (Paucibacillary/PB leprosy) still poses as quite a challenge. Although PCR-based tests provide higher sensitivity and specificity than enzyme-linked immunosorbent assay (ELISA), it would be quite impractical for daily practice. Current research

prioritizes on specific molecular identification for *M. leprae* and development of sensitive laboratory tests to diagnose asymptomatic cases or the ones with fewer symptoms, as well as predicting the development of disease among exposed individuals.⁶⁻⁸

A problem that interferes with the attempt to tackle leprosy is the stigma or negative outlook on the patients and their families. This stigma also causes the sufferer to refrain from seeking treatment out of fear for their condition being known by their peers. Indeed, it's necessary promoting strategies to cut off the chain of transmission that can spreading this infection and aggravating the occurrence of disability in leprosy patients.⁵

Early diagnosis of leprosy is critical to make sure the sufferers receive adequate Multi-Drug Therapy (MDT) treatment appropriate to the type of leprosy as government regulations. A precise early diagnosis and treatment are key elements in breaking the chain of transmission and preventing disability on the patients.⁷ Thus, this review will further discuss the diagnoses, additional examinations, and therapies for leprosy.

REVIEW

Leprosy is a chronic granulomatous infection caused by intracellular obligate *Mycobacterium leprae*

bacilli, which tends to attack the skin and peripheral nerves, causing neuropathy, chronic abnormalities, and disability. Depending on the type of leprosy, the involvement of the reticuloendothelial system, bone and joint, eyes, testicles, muscles, adrenals, and other areas may occur. The transmission of leprosy takes place between humans through long-term and close contact with untreated MB-typed patients.^{6,9,10}

WHO has been collecting data on the prevalence of leprosy each year, covering new and treated cases. According to WHO, in 2017, India, Brazil, and Indonesia cumulatively recorded 80.2% new leprosy cases. In Indonesia, the number of new cases decreased from 17,202 in 2015 to 16,826 in 2016 and further decreased to 15,910 in 2017. The highest number of new cases was in 2011 with 20,023 cases.^{3,4}

According to its clinical, histopathological, and immunological criteria, leprosy is grouped into 6 forms using the Ridley-Jopling classification (1962), which are Tuberculoid (TT), Borderline Tuberculoid (BT), Borderline-borderline (BB), Borderline-lepromatous (BL), Subpolar Lepromatous (LLs), and Polar Lepromatous (LLp). To facilitate its treatment, leprosy is divided into 2 groups according to WHO, the paucibacillary (PB) and multibacillary (MB) type.^{1,9,11}

Table 1. The clinical appearance of leprosy^{1,9}

Feature	Tuberculoid	Borderline tuberculoid	Midborderline	Borderline lepromatous	Lepromatous
Number of lesions	1 or more than 3	More than 10	10–30	Lots, asymmetrical (>30)	Copious, symmetrical
Size	Varies, usually large	Varies, several lesions are larger	Varies	Small, some are larger	Small
Surface	Dry, scaly	Dry, scaly	Rather rough, rather shiny	Smooth, shiny	Smooth, shiny
Anesthesia	Obvious	Obvious	More obvious	Unclear	Usually unclear
AFB	Negative	Negative or 1+	1–3+	3–5+	Lots, globus are present (6+)
Lepromin test	Strongly positive	Weakly positive	Negative	Negative	Negative

The clinical diagnosis is confirmed if two out of three criteria are present, or there are AFB bacteria in the skin scraping, or a typical histological characteristic for leprosy is found. The cardinal signs for leprosy include (1) Hypopigmentation or erythematous skin lesions, such as macule or plaque, accompanied by the loss of sensation on the skin; (2) Thickening or enlargement of peripheral nerves and signs of its

damage, such as loss of sensory, paralysis, or motoric dysfunction with or without nerve enlargement; (3) The presence of acid-fast bacilli (AFB) on skin lesion scraping and/or biopsy. Early and precise diagnosis of leprosy is critical in preventing irreversible damage to the nerves.^{8,12-14}

Two predominating characteristics of suspected leprosy patients are the type of lesion and its

distribution on the body. Under the context of diagnosis purposes, the variable nature of leprosy will greatly aid in pin-pointing the symptoms on the skin.¹⁵ A single or several grouped macules represents an unclear or intermediate leprosy diagnosis. In addition to the intermediate leprosy clinical manifestation, the occurrence of several macules might be an early stage of lepromatous leprosy. Therefore, it is strongly advised to do a bacteriological examination of specimens from these kinds of lesion.¹⁵

A tuberculoid lesion is solitary and few (less than 5) with either unilateral to bilateral distribution or asymmetrical. The lesion might appear hypopigmented or erythematous. A tuberculoid lesion typically occurs as a wide erythematous plaque with well-demarcated edges, elevated border, and a flat center. The most commonly affected areas are the face, extremities, trunk, axilla, groin, and perineum. A tuberculoid lesion is anesthetic or hypoesthetic and anhidrotic, accompanied by an enlargement of the proximal superficial peripheral nerve of the lesion.^{15,16}



Figure 1. Tuberculoid Leprosy: single lesion, anesthetic and annular.^{2,11}



Figure 2. Borderline leprosy: Elevated facial lesion.¹³

The tuberculoid borderline lesion is similar to that of tuberculoid lesion, only with smaller size and larger quantity. Paucibacillary lesion tends to scatter and might be grouped. The skin tends not to produce sweat, causing the affected surface to appear dry and coarse. Macules and plaques might appear ring-like, indicating the occurrence of central healing. Papules might appear grouped, forming a plaque or a border of macule or annular lesions. Around the larger lesions (BT), where the edges are less demarcated, smaller satellite lesions might appear. Enlarged or protruding nerves might be palpated near larger infiltrated lesion.¹⁵

There are more lesions in borderline leprosy (still countable), which consist of irregular red plaques. A smaller satellite lesion surrounds the larger plaque asymmetrically. The lesion's borders are less demarcated than the tuberculoid type, and there might be nerve enlargement.^{15,16} Borderline lepromatous (BL) type has a symmetrical, copious lesion, and might consist of macules, papules, plaques, and nodules. The number of small lesions on the lepromatous type exceeds that in any other borderline type. Nerve involvement appears afterward. The nerve will enlarge, become painful, or both. The patients usually do not exhibit typical characteristics as seen in lepromatous leprosy such as madarosis, keratitis, nasal ulceration, and leonine facies.¹⁶

The lepromatous leprosy cutaneous lesion consists of pale macules or diffuse infiltration on the skin. The macule lesions are symmetrically scattered, small-sized, and copious, in contrast to a tuberculoid lesion, which is larger and fewer. In macules, there is no alteration in skin texture, and it blends with the surrounding skin. The sensation is not diminished or might be lessened slightly on the lesion, no nerve enlargement, and no sweat alteration. There is a loss of the outer third of the eyebrows, followed by eyelashes and trunk hair. However, there is no alteration on the scalp hair.^{15,16}

Sensory loss on the lesion area and the distal extremities needs to be checked using cotton, nylon thread, or pen tip examination. The three modalities, touch, pain, and temperature function have to be evaluated as well. Due to the rich nerve supply on the face, sensory alteration tends to be unclear in this area compared to other body parts. The diagnosis of PB, particularly tuberculoid leprosy, depends on those simple procedures. The presence of one or more chronic skin lesion accompanied by anesthesia or hypoesthesia directs the diagnosis to leprosy.¹³

There are currently no laboratory tests considered adequate for the diagnosis of leprosy. The additional examination consists of slit-skin smear, serological, histopathological, molecular examination and also

other tests such as the Mitsuda intradermal reaction can help establish the diagnosis in doubtful cases. Slit skin smear examination is a simple microscopic examination to see the presence of acid-resistant bacteria. This test is easy to do and gives good results if done by experienced staff. Slit-skin smear examination is useful in the stages of diagnosis, classification, monitoring of treatment and observation the disease severity.¹⁸ However, this examination cannot detect leprosy before the number of bacilli reaches a certain amount. So a negative slit-skin smear may not necessarily exclude leprosy. Therefore, a test with better sensitivity might be needed to detect *M. leprae*.^{7,19,20} Skin biopsy is a histopathological examination with adequate accuracy in lesion

classification. A biopsy is useful to confirm diagnosis, prognosis, and evaluate the therapy. A peripheral nerve biopsy is a useful tool in diagnosing leprosy whenever physical examination and a skin biopsy is inconclusive. The histopathological characteristic of tuberculoid leprosy is the presence of epithelial cell granulomas. This is under the presumption that the *M. leprae* lies on the Schwann cells of the nerve, particularly on colder areas, places of trauma, or superficial parts of trapped nerves. Nerve lesion on lepromatous leprosy (LL) is characterized by bacterial multiplication without inhibition, mainly on Schwann cells, due to the lack of efficient cellular immunity against *M. leprae*. In BB-LL leprosy, there is focal and diffuse nerve involvement.^{13,21,22}

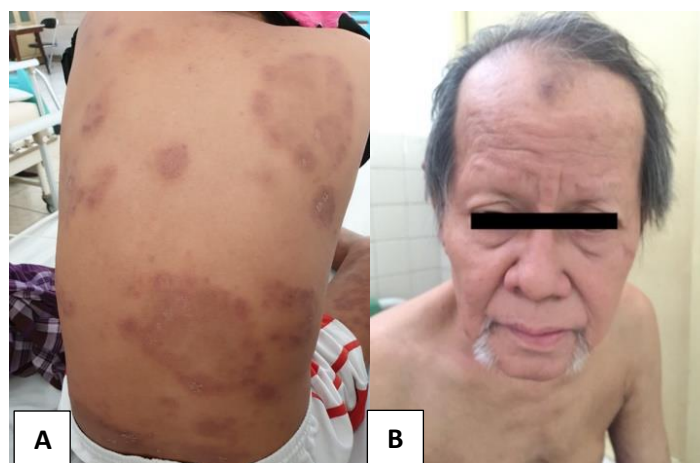


Figure 3. Borderline lepromatous leprosy: Multiple scattered plaques (A). Lepromatous leprosy: madarosis (B).^{2,13}

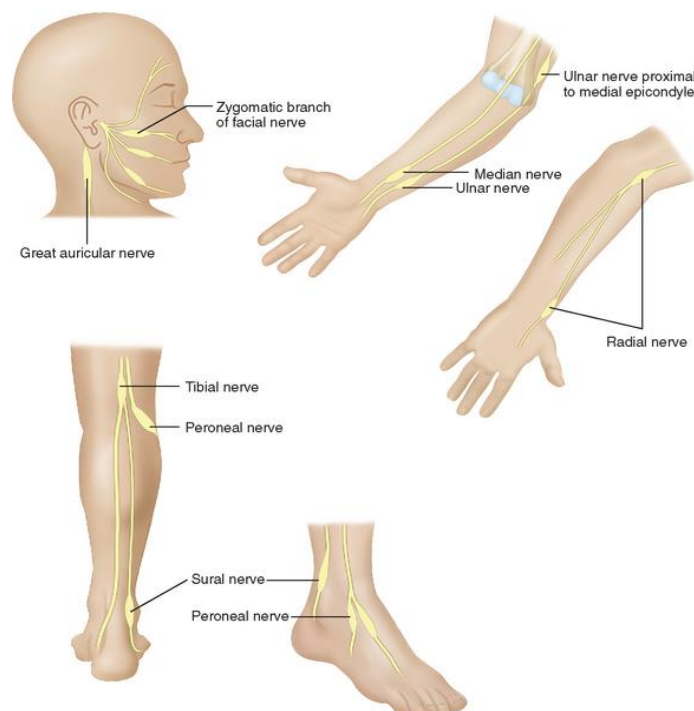


Figure 4. The most commonly affected nerves in leprosy.¹⁷

Immunohistochemistry reaction using a monoclonal or polyclonal antibody to detect *M. leprae* antigen promises better sensitivity and specificity compared to conventional methods, an important tool in diagnosing leprosy, particularly on early phase or in PB leprosy. Some antibodies are used in the diagnosis, for example, the ones directed to protein (e.g., S-100 and heat shock protein such as 35 kDa and 65 kDa), and against lipoarabinomannan and phenolic glycolipid-1 (PGL-1). Except for anti-PGL-1 antibody, which is directed to the specific antigen for *M. leprae*, and the remaining antibodies can trigger a positive result in normal skin or several chronic communicable or autoimmune disease.⁷

In some patients, these nerves are damaged beyond recognition under routine histopathological examination. A coil of spindle-shaped Schwann cells might be difficult to distinguish from a group of epitheloid. S-100 dye that selectively colors Schwann cells might be used to release remaining damaged nerves in the tuberculoid granuloma. Some publications highlight the dye's benefits in diagnosing tuberculoid leprosy and distinguishing them from other tuberculoid granulomas on the skin such as tuberculosis, deep fungal infection, and sarcoidosis. Positive staining might eliminate leprosy if it shows intact nerve end due to other granulomatous diseases.⁷ Monoclonal antibody (Mab), MLO4, which reacts explicitly with 35 kDa epitope of *M. leprae*, is used to detect antibodies in leprosy patients. With this test, nearly 100% of active BL/LL and more than 40% TT/BT patients bear positive result.^{23,24,25,26,27}

Pemeriksaan serologis kusta adalah pilihan yang murah, mudah, dan bisa dilakukan di lapangan. Pada saat ini pemeriksaan serologis terhadap antibody PGL-1. The chemical structure of an antigen has been discovered, particularly PGL, aiding in the revolution in leprosy serodiagnostic, which turns out, can be found in *M. leprae*-infected armadillo tissues. Some studies have evaluated the benefit of PGL-1 in estimating the probability of a contact that becomes leprosy patient. A positive PGL-1 in contact carries three times the risk of developing leprosy. The presence of anti-PGL-1 antibody aids in classifying the

clinical feature, in which MB patients exhibit higher antibody titer while PB shows little to none, with the PGL-1 seropositive patient percentage ranges from 80-100% in lepromatous leprosy and 30-60% in tuberculoid leprosy. Increased PGL-1 antibody in treated patients indicates the recurrence of the disease. The PGL-1 antigen is water-insoluble; therefore, it stays in tissues for quite a long time, which in turn triggers IgM antibody production in the absence of living bacilli. Thus, the presence of anti-PGL-1 antibody does not necessarily mean an active disease.^{7,28,29,30,31}

Serological tests using antigens other than phenolic glycolipids-I (PGL-I) which are also widely studied include analogs in trisaccharide, NDO and NTP. In addition, diagnostic markers include antibodies to Leprosy IDRI Diagnostic-1 (LID-1), which is a blend of ml0405 and ml2331 gene products, as well as antibodies against NDO-LID, the conjugate of natural octac disaccharide (NDO) and LID. Recently, the conjugation between natural octac disaccharide (NDO) and IDRI leprosy diagnostic (LID) -1, known as NDO-LID, shows great possibility because of its high specificity and sensitivity and ability to detect leprosy before any clinical signs.^{32,33}

Another examination includes polymerase chain reaction (PCR), a simple and sensitive diagnostic tool used to detect, measure, and determine the viability of *M. leprae*, which significantly shows better results than other general microscopic examinations. This is based on specific sequence amplification of the *M. leprae* genome and deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) fragments identification. PCR allows early confirmation, PB and pure nerve leprosy, subclinical contact infection, therapy evaluation, recovery decision, or identification of resistant individual against MDT, and aids in understanding the mechanism of *M. leprae* transmission. PCR can detect *M. leprae* even before symptoms occur in the high-risk group (contact within the household). *M. leprae* investigation by PCR has been done with various samples, such as swabs, fragment biopsy, or skin biopsy, nasal swab, urine, nerve, lymph nodes, and hair.^{7,20,34,35,36,37}

Table 2. Multi-Drug Therapy for Paucibacillary type

Drugs	<10 years	10–15 years	>15 years	Note
Rifampicin	300 mg/month	450 mg/month	600 mg/month	Taken in front of an officer
Dapsone	25 mg/month	50 mg/month	100 mg/month	Taken in front of an officer
	25 mg/day	50 mg/day	100 mg/day	Taken at home

Duration of therapy: treatment is given in 6 doses during 6–9 months^{9,16,38,39}

Table 3. Multi-Drug Therapy for Multibacillary type

Drugs	<10 years	10–15 years	>15 years	Note
Rifampicin	300 mg/month	450 mg/month	600 mg/month	Taken in front of an officer
Dapsone	25 mg/month	50 mg/month	100 mg/month	Taken in front of an officer
	25 mg/day	50 mg/day	100 mg/day	Taken at home
Clofazimine (Lamprene)	100 mg/month	150 mg/month	300 mg/month	Taken in front of an officer
	50 mg twice a week	50 mg once every 2 days	50 mg/day	Taken at home

Duration of therapy: treatment is given in 12 doses in 12-18 months^{9,16,38,39}

Leprosy is treated with MDT WHO (1998, 2012). The MDT regimen is adjusted according to the type of disease, PB, and MB.

Rifampicin is a semisynthetic derivate of Rifamycin, an antibiotic acquired from *Streptomyces mediterranei* bacterial fluid suspension. Rifampicin should not be given as monotherapy due to its resistance-triggering effect. This medication possesses potent antibacterial property, eradicating more than 99.99% *M. leprae* bacteria with its single dose of 1500 mg or as 3 to 4 daily doses of 600 mg. Rifampicin causes an alteration in urine, ear, and sweat color into red-orange without any further consequence; however, patients have to be informed prior to taking the first dose. Rifampicin is able to penetrate through the blood-brain barrier and placenta. Due to its solubility in fat, rifampicin permeates through cell membranes,

supporting its effectiveness in eradicating intracellular bacteria.^{19,40,41,42,43}

The clinical effect of rifampicin can be seen quickly. In lepromatous leprosy, defects on the nose will lessen in 2 to 3 weeks, while skin lesion subsides within 2 to 3 months. Skin preparation coloring will show a rapid decline in its morphological index. In bacil coloring, there will be no bacteria seen within 4 to 6 weeks of Rifampicin treatment. *M. leprae* acquired from biopsy samples will show no surviving bacteria after 4 to 7 days of treatment.^{40,44}

Intolerance to Rifampicin might be due to allergy, comorbidities such as chronic hepatitis, or Rifampicin-resistant bacterial infection. Patients who are infected with Rifampicin-resistant bacteria are usually also resistant to Dapsone. Therefore, there is an alternative regimen as follows.^{9,16,45}

Table 4. Regimen for patients who cannot take Rifampicin^{9,16,43}

Duration	Drug Type	Dose	
First 6 months	Clofazimine	50 mg/day	
	added with 2 out of the following 3 drugs:		
	Ofloxacin		400 mg/day
	Minocycline		100 mg/day
Continued for 18 months	Clarithromycin	500 mg/day	
	Clofazimine with ofloxacin	50 mg/day 400 mg/day	
	OR Minocycline	100 mg/day	

Dapsone (4.4 diaminodiphenyl sulfone) is a sulfa group drug first synthesized in 1908. Dapsone-the main ingredient of derivatives-diaminodiphenyl sulfone (DDS/dapsone) is currently accepted as an active molecule. Since the early 60s, Dapsone has been continuously utilized as the main drug against leprosy. The normal dose of Dapsone for adults is 100 mg/day and 2 mg/kg/day for children. Its half time is approximately 24 hours. In multibacillary (borderline

and lepromatous type) leprosy, the clinical response will be visible within 3–6 months after the initial Dapsone therapy. However, complete clinical regression will need longer time, usually up to 2 to 3 years.^{40,41}

The clinical response of paucibacillary (TT and BT) leprosy patient quite varies; about 2/3 of patients experience complete healing within 6 months, while the rest might need more than 1 year to regress. Nerve

deficit is mostly unaffected by Dapsone. Therefore, the eyes and extremities need to be protected against trauma and burn injuries. Dapsone has a side effect, just as seen in hemolytic anemia, as well as potentially induce liver failure in some patients. The renal and liver function might be abnormal during the examination. In some cases, yellow coloration or jaundice might appear along with hepatic enlargement. It is important to mention the presence of liver damage in leprosy patients, mainly in lepromatous type, that might be caused by viral hepatitis, commonly found in leprosy endemic areas.^{40,47}

A hypersensitivity reaction in the form of Dapsone syndrome is often seen in patients after several months of treatment. Reports have shown that the frequency increases to more than 95% of the number of cases, that is 108 cases, that occurred within the last 2 decades, mostly occurring since MDT was first introduced. Dapsone causes serious side effects such as Dapsone syndrome (drug hypersensitivity syndrome), therefore its use needs to be halted. There is no modification for MB patients; hence MDT is continued without Dapsone for 12 months. Meanwhile, in PB leprosy therapy, Dapsone is replaced with Clofazimine under the same dose as MDT for MB for 6 months.^{9,40,48}

Clofazimine has a mild antibacterial property against *M. leprae*, its effect is a bit weaker than that of Dapsone. Studies have shown that Clofazimine accumulates in the macrophage, where *M. leprae* resides, triggering local hydroxyl and superoxide radical formation. These products inhibit *M. leprae* bacterial multiplication. The clinical response of daily 50 to 100 mg of Clofazimine is similar to that in 100 mg of Dapsone, although its effect is a bit weaker. Clofazimine has a long half time; hence its supervised monthly dose of 300 mg is also included in the regimen for multibacillary leprosy as recommended by the WHO. Almost all types of leprosy respond well to this drug, indicating its benefit. However, Clofazimine should not be used as either monotherapy or a replacement for Dapsone that is cheaper and more effective.^{40,41,49}

Upon Clofazimine consumption, there might be an alteration of the skin color into red-brownish because its deposition on the skin increases pigmentation, which is a common finding. If the patient refuses to take Clofazimine, it can be replaced with 100 mg/day of Minocycline in the 12 months of MDT regimen or 400 mg/day of Ofloxacin for 12 months or 600 mg/month of Rifampicin, 400 mg/month of Ofloxacin, and 100 mg/month of Minocycline for 24 months.^{9,16,50}

CONCLUSION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, an intracellular obligate bacterium. It mainly attacks peripheral nerve and skin. Indonesia is in the top three countries, along with India and Brazil, with the most leprosy cases worldwide. East Java has the highest number of new leprosy cases in Indonesia. The transmission takes place between humans through long-term and close contact with the untreated patient in the multibacillary type.

To confirm the diagnosis, there are cardinal signs for leprosy. Slit-skin smear remains the main choice of additional examination for leprosy. However, this method is still not as sensitive as expected for PB type. Additional examinations to confirm diagnosis and classification are skin and nerve histopathology, serology test, histochemistry reaction, and PCR. A precise diagnosis for leprosy, either physical or additional examination, is crucial to determine the Multi-Drug Therapy (MDT) regimen and break the chain of transmission.

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