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EPIDEMIOLOGICAL AND ETIOPATHOGENESIS ASPECTS OF LEPROSY

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ABSTRAK

Penyakit kusta merupakan penyakit menular yang disebabkan oleh bakteri basil tahan asam yaitu *Mycobacterium lepra*. Masuknya *Mycobacterium leprae* ke dalam tubuh dapat memicu berbagai respon imun. pada beberapa individu, respon imun yang adekuat dapat mencegah perkembangan penyakit ini, namun pada individu lain dapat berkembang menjadi bentuk yang parah sehingga dapat mengakibatkan kecacatan. Penyakit kusta tersebar luas di seluruh dunia, terutama di daerah tropis/subtropis. Angka kejadian tertinggi terdapat di India, Brazil, dan india. Pemberantasan penyakit ini masih menjadi tantangan, terutama di daerah endemis seperti Indonesia. Oleh karena itu, artikel ini bertujuan untuk mengulas konsep dasar penyakit kusta, terutama dalam aspek epidemiologi dan etiopatogenesis, sehingga dapat dijadikan referensi untuk penelitian lebih lanjut.

ABSTRACT

Epidemiological and Etiopathogenesis Aspects of Leprosy. Leprosy is an infectious disease caused by the acid-fast bacillus, namely *Mycobacterium lepra*. The entry of *Mycobacterium leprae* into the body can trigger various immune responses. in some individuals, an adequate immune response can prevent the development of this disease, but in other individuals it can develop into a severe form that can result in disability. Leprosy is widespread throughout the world, especially in tropical/subtropical areas. The highest incidence rates are in India, Brazil and India. Eradicating this disease is still a challenge, especially in endemic areas like Indonesia. Therefore, this article aims to review the basic concepts of leprosy, especially in the epidemiological and etiopathogenesis aspects of leprosy, so that it can be used as a reference for further research.

INTRODUCTION

Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*, which primarily attacks the peripheral nerves and secondarily the skin and other organs. Most infected people are asymptomatic, but a small proportion are symptomatic and have a tendency to become disfigured, especially on the hands and feet. Leprosy is a chronic disease that can cause serious disability problems in affected individuals. Stigma in the community leads to leprosy sufferers being ostracized. The problems are not only physical, but also psychological, economic and social.[1]

The prevalence of leprosy worldwide is still relatively high, especially in Indonesia, which is one of the leprosy endemic areas. Leprosy is widespread throughout the world, especially in tropical/subtropical regions, can affect all ages, and is more common in men than women. In 2020, there were 127,558 new cases worldwide. The highest incidence is in India, Brazil, and Indonesia. In Indonesia, leprosy is found in almost all provinces with an uneven distribution pattern. Although by mid-2000 Indonesia had achieved national leprosy elimination, from 2002 to 2006 there was an increase in new leprosy patients. In 2006, the number of new leprosy patients in Indonesia was 17,921. The provinces reporting the highest number of new leprosy patients were Maluku, Papua, North Sulawesi and South Sulawesi with prevalence greater than 20 per 100,000 population. In 2010, there were 17,012 new cases of leprosy in Indonesia with a prevalence rate of 7.22 per 100,000 population while in 2011, there were 19,371 new cases of leprosy in Indonesia with a prevalence rate of 8.03 per 100,000 population.[2] In 2020, there were 11,173 new cases of leprosy in Indonesia, 86% of which were multibacillary (MB) leprosy.[1]

Leprosy has a long incubation period (measured in years), starting from *M. leprae* infection to the appearance of signs and symptoms. It is assumed that there is a subclinical/latent stage of infection following *M. leprae* infection, which can subsequently lead to overt signs and symptoms of leprosy. A test to identify such latent infection would be useful to identify people who could benefit from preventive interventions. However, a systematic review of the usefulness of predictive tests for diagnosing latent leprosy found that many did not report long-term follow-up, and among studies with several years of follow-up, there was poor accuracy in identifying people who would develop leprosy. Therefore, WHO states that currently available tests to identify contacts who have been infected by *M. leprae* are not sufficiently accurate and does not recommend their use.[3] The entry of *M. leprae* into the body can trigger various immune responses. in some individuals, an adequate immune response can prevent the development of this disease, but in other individuals it can develop into a severe form that can result in disability.

METHOD

The method used is a literature review to find, assess, and evaluate published works of in-depth thought and investigation. Using national and international journal websites including Google Scholar, Science Direct, Elsevier, EBSCO, Medline, PubMed, Proquest, and Wiley, the library materials used to prepare this literature review were found. The author employed Boolean operators (AND, OR) and the keywords leprosy, infectious disease, epidemiology, etiopathogenesis, and Mycobacterium leprae in the search.

The procedure of choosing pertinent references was made easier by the application of many inclusion criteria. Among the requirements for inclusion are the following: 1) Articles that contain keywords and subjects related to the title and theme of the literature review. 2) Books and papers in literature released between 2003 and 2023 that are available in full text in scholarly and PDF formats (peer reviewed journals). If the article's topic and content are deemed significant and no other publications have reviewed it within the allotted time frame, then a few pieces published before 2003 are nevertheless accepted as references. 3) Both Indonesian and English are available in the chosen books and journal articles. 4) An original article or a literature review containing keywords and themes that align with the review's theme and title is the sort of article reference. References in the form of unpublished publications are excluded from this literature review as an exclusion criterion.

RESULT AND DISCUSSION

Aspect of Epidemiology

The number of people with leprosy is still high. In 2020, there were 127,558 new cases worldwide.[4] The highest incidence is in India, Brazil and Indonesia.[5] Leprosy is spread throughout the world, especially in tropical and subtropical regions. It can affect all ages, with the highest frequency in the age group between 30-50 years and is more common in men than women.[1]

In 2015, the number of newly diagnosed leprosy cases was 210,758 worldwide. The figure has remained largely constant over the past decade (for comparison, there were 265,661 cases in 2006). New leprosy case finding is highest in Brazil, at >10 per 100,000 population. New leprosy case finding in Indonesia in 2015 was 1-10 per 100,000 population. Figure 1 shows the distribution of new leprosy cases worldwide based on data from the World Health Organization (WHO). New cases of leprosy are found in South America, Africa and Southeast Asia.[5,6]

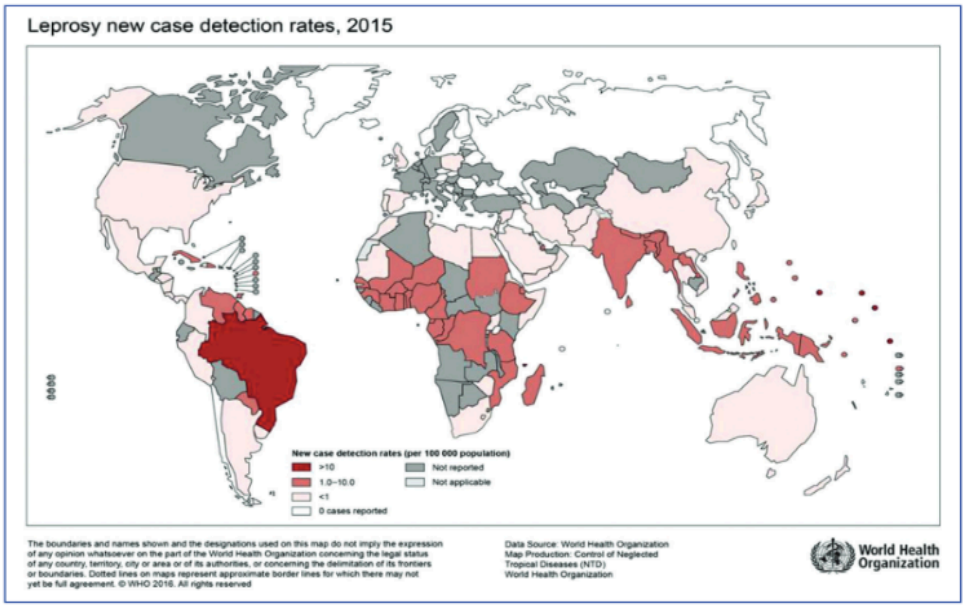

Figure 1. New cases of leprosy worldwide.[5] New cases of leprosy are mostly found in South America, Africa and Southeast Asia. The rate of new leprosy cases in Indonesia in 2015 was 1-10 per 100,000 population.[6]

Compared to 2020, the incidence of new cases of leprosy does show a decreasing trend, but it shows that leprosy transmission persists despite efforts by WHO and various national health programs. Although the goal set by WHO in 1991 to eliminate leprosy by the year 2000 has not been achieved, the success of control measures coordinated by WHO has been a breakthrough in every respect, especially after the introduction of multi-drug therapy.[7] Currently, 95% of all newly registered leprosy cases are reported from 14 countries, the highest incidence being seen in India, Brazil, and Indonesia, followed by the Democratic Republic of Congo, Ethiopia, Madagascar, Mozambique, Nigeria and Tanzania in Africa; Bangladesh, Myanmar, Nepal, Sri Lanka and the Philippines in Asia.[1]

In Indonesia, leprosy is found in almost all provinces with an uneven distribution pattern. Although by mid-2000 Indonesia had achieved national leprosy elimination, from 2002 to 2006 there was an increase in new leprosy patients. In 2006, the number of new leprosy patients in Indonesia was 17,921. The provinces reporting the highest number of new leprosy patients were Maluku, Papua, North Sulawesi and South Sulawesi with prevalence greater than 20 per 100,000 population. In 2010, there were 17,012 new cases of leprosy in Indonesia with a prevalence rate of 7.22 per 100,000 population while in 2011, there were 19,371 new cases of leprosy in Indonesia with a prevalence rate of 8.03 per 100,000 population.[2]

The leprosy prevalence rate in Indonesia in 2020 was 0.49 cases/10,000 population and the new case finding rate was 4.12 cases per 100,000 population. Over the last ten years, the incidence trend has been decreasing, both in the prevalence rate and the new case finding rate of leprosy. In 2020, 11,173 new cases of leprosy were reported, 86% of which were multibacillary (MB) leprosy.[2]

Aspect of Etiology

The agent that causes leprosy is *Mycobacterium leprae* which was discovered by GH Armauer Hansen, a Norwegian scholar in 1873. This germ is acid-resistant, rod-shaped with a size of 1-8 microns and a width of 0.2 - 0.5 microns, usually in groups and some are scattered one by one, lives in cells, especially cold temperature tissues and cannot be cultured in artificial media (Figure 2). It can also cause systemic infections in armadillos.[8]

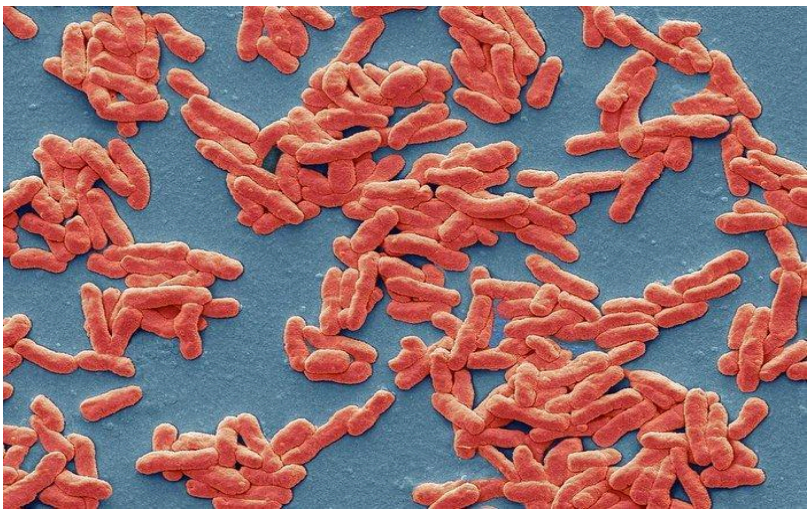

Figure 2. *Mycobacterium leprae* bacteria. These bacteria are acid-resistant, rod-shaped with a size of 1-8 microns and a width of 0.2 - 0.5 microns, usually in groups.[8]

Aspect of Pathogenesis

Mycobacterium leprae is a bacterium with low pathogenicity and invasiveness. This is known due to the fact that people with more of the bacteria may not always show more severe symptoms; in certain cases, it may even be the opposite. Different immune responses in different people can trigger localized or global granuloma reactions in a limited or progressive manner, which is what causes the imbalance between the infection rate and the disease rate. Leprosy is a disease of the immune system, the clinical symptoms are more closely related to the degree of cellular reactivity than the severity of infection in the patient. In the course of the disease, a leprosy patient may experience a leprosy reaction.[9]

Two routes of entry of *M. Leprae* into the human body are currently known, namely through the skin and the upper respiratory tract. The estimated incubation period is between three and ten years.[9] One study suggested that an incubation period of 10 years is required for the lepromatous type and 4 years for the tuberculoid type. It is more difficult to demonstrate an epidemiologic link between specific exposures and disease onset because of the unusually slow mycobacterial multiplication rate of every two weeks.[10] According to WHO, the onset of symptoms may last from 1 to 20 years or more.[11]

The most likely method of spreading the bacilli is hematogenously. *M. leprae* bacteria can be found on buffy-coat preparations, but usually without fever or other systemic signs. The bacteria can infect and live for at least a short time in deep tissues and inflammatory cells associated with the organism, especially those in nerve trunk segments located near the skin. 19,21 In general, *M. leprae* invades Schwann cells in the innervation and macrophages in the skin. *M. leprae* bacilli can be distinguished from other gram-positive and gram-negative bacteria by the presence of mycolic acid and phenolic glycolipid-1 (PGL-1) in their lipid-rich cell walls. Phenolic glycolipid-1 mediates the entry of bacilli into macrophages through CR1, CR3, and CR4 receptors on the C3 component of complement, triggering phagocytosis. It is an important element in the etiology of the disease and is involved in the mechanism of lysosomal release that plays an immunosuppressive effect to aid the survival of *M. leprae* inside macrophages, its host cells.[10]

Schwann cells play an important role in the immune response to *M. leprae* as they can process and present antigens to CD4 cells, which then initiate an inflammatory process that is detrimental to these cells and causes demyelination of peripheral nerves and neurological lesions. By causing the production of trans-membrane TNF-∝ and TNF receptors in Schwann cells, M. leprae also enhances the inflammatory response by increasing the susceptibility of these cells to the pro-inflammatory cytokine TNF-∝.[10]

According to the Th1/Th2 leprosy paradigm, individuals with tuberculoid leprosy show higher expression of Th1 cytokines (such as IL-7 and IL-15) while individuals with lepromatous leprosy show higher expression of Th2 cytokines (such as IL-4, IL-5, IL-10, and TGF-β). According to peripheral blood analysis of leprosy patients, there is a predominant induction of Th1 cytokine secretion (IFN-γ, IL-2, and IL-12) in pausibacillary presentation and Th2 cytokine secretion (IL-4, IL-5, IL-6 and IL-10) in multibacillary presentation after stimulation with recombinant *M. leprae* antigens.[10,12]

Leprosy reactions are systemic reactions that can occur long before treatment starts, during treatment, or even long after treatment ends. There are two different types of leprosy response, T1R (reversal reaction) and T2R, also known as erythema nodosum leprosum (ENL). T1R is involved in patients with borderline type manifested as exacerbation

of erythema and tenderness of pre-existing lesions, often accompanied by marked acroedema. The presence of an inflammatory infiltrate dominated by CD4+ T cells, differentiated macrophages and thickened epidermis has been observed in reversal reactions. Whereas, T2R is usually involved with the lepromatous type manifested as a reaction that usually occurs suddenly, with the onset of skin redness and soft pustules in various parts of the body accompanied by systemic symptoms, such as fever, weakness, enlarged lymph nodes, anorexia, weight reduction, arthralgia, and edema. There may be a marked leukocytosis in this reaction, which usually resolves after the reaction is over. The presence of high levels of proinflammatory cytokines such as TNF-, IL-6, and IL-1β in the serum of ENL patients suggests that these pleiotropic inflammatory cytokines at least partially contribute to the clinical manifestations of type II responses.[12–14]

The diagnosis of leprosy is based on the following: clinical examination, with or without a slit-skin smear or pathological examination of a biopsy. The diagnosis of leprosy in current practice is based on the presence of at least one of three cardinal signs, namely:[3]

1) Numb skin lesions (abnormalities). A skin disorder/lesion that may take the form of a whitish (hypopigmentation) or reddish (erythema) patch that is numb (anesthesia).
2) Peripheral nerve thickening accompanied by impaired nerve function. This peripheral nerve function disorder is usually the result of chronic inflammation of the peripheral nerves (peripheral neuritis). The disorders of peripheral nerve function are in the form of sensory function disorders, namely numbness, and motor function disorders, namely muscle weakness (paresis) or paralysis (paralysis).
3) The discovery of *M. leprae* on bacteriological examination.

In latent cases, there are no recommended tests to diagnose leprosy infection (latent leprosy) among asymptomatic contacts. Evaluation of potential tests for *M. leprae* infection requires longitudinal follow-up to determine the incidence of clinical leprosy, to determine the predictive utility of the test.

Leprosy can be classified based on clinical manifestations (number of lesions, number of nerves affected), results of bacteriologic examination, histopathologic examination and immunologic examination. Classification aims to determine treatment regimens, prognosis and complications. Then for operational planning, such as finding patients who transmit and have high epidemiological value as the main target of treatment. Furthermore, for the identification of patients who are likely to suffer from disability due to leprosy. There are many types of leprosy classifications including the Madrid, Ridley-Jopling, and WHO classifications.

In the Madrid classification, leprosy is divided into Indeterminate (I), Tuberculoid (T), Borderline-Dimorphous (B), Lepromatous (L). This is the simplest classification based on clinical manifestations, bacteriological examination, and histopathological examination, as recommended by the International Leprosy Association in Madrid in 1953.[15]

In the Ridley-Jopling classification, leprosy is a clinical spectrum ranging from those with low immunity on one side to those with high immunity to *M. leprae* on the other. An individual's cell mediated immunity (CMI) determines whether he or she will develop leprosy when infected with *M. leprae* and the type of leprosy he or she will develop on the leprosy spectrum. This classification system is widely used in leprosy research, as it can

explain the relationship between germ interaction and a person's immunological response, especially the specific cellular immune response. The five types of leprosy according to Ridley-Jopling are lepromatous type (LL), borderline lepromatous type (BL), mid-borderline type (BB), borderline tuberculoid type (BT), and tuberculoid type (TT).[15]

In 1982, WHO developed a classification to facilitate treatment in the field. In this classification, all leprosy patients are only divided into 2 types: Pausibacillary (PB) and Multibacillary (MB). The classification can be seen in tables 1. To date, the Indonesian Ministry of Health has adopted the WHO classification as a guideline for the treatment of leprosy patients. The basis of this classification is based on clinical manifestations and bacteriological examination results.[2,3]

Table 1. Classification/type of leprosy according to WHO

Sign	PB	MB
Leprosy patches	Amount 1 to 5	Amount more than 5
Peripheral nerve thickening accompanied by impaired function (impaired function can be in the form of lack of feeling or weakness of the muscle innervated by the nerve concerned.	Only one nerve	More than one nerve
Bacteriological examination	No acid-resistant bacilli found (negative)	Acid-resistant bacilli found (positive)

Multidrug therapy (MDT) is a combination of two or more anti-leprosy drugs. Rifampicin is an anti-leprosy drug that has a strong bactericidal effect, while other anti-leprosy drugs are bacteriostatic. It comes in 4 different blister forms depending on the patient's age group and leprosy type (adult PB, adult MB, pediatric PB, and pediatric MB). The procedure for taking MDT is that the first day's dose is taken in front of the health center, clinic, or hospital staff where the patient is treated, then the medicine is taken home and the patient must take the medicine with family supervision. The purpose of treatment is to stop transmission in the community, prevent drug resistance, improve patient regularity in treatment, and prevent the occurrence of a disability (disability) or so that previously existing disabilities will not increase in the future.[16]

The groups of people who need MDT are patients who are newly diagnosed with leprosy and have not previously received MDT and patients who are included as repeat leprosy sufferers, namely relapsed leprosy patients, patients who are returning to treatment after previously dropping out or defaulting, patients who have changed their place of treatment, or there is a change in the classification or type of leprosy.

According to PMK No. 11 of 2019 concerning Leprosy Management, the MDT treatment regimen applicable in Indonesia follows the WHO recommendations, which are as follows:

1) Pausibacillary (PB) leprosy

PB leprosy patients are medicated based on age classification. The patient will take the medication for 6-9 months, where one blister is taken for a period of 28 days, so the patient will need 6 blisters of MDT in one course of treatment.

2) Multibacillary (MB) leprosy

Medication for MB leprosy patients is given based on age classification. Patients will take the medication for 12-18 months, where one blister is taken for a period of 28 days, so the patient will need 12 blisters of MDT in one course of treatment.

CONCLUSION

The prevalence of leprosy is still high, especially in Indonesia, which is the 3rd highest country with the most leprosy sufferers. This disease is caused by *Mycobacterium leprae*, which is an acid-fast bacillus. The entry of *Mycobacterium leprae* into the body can trigger various immune responses. in some individuals, an adequate immune response can prevent the development of this disease, but in other individuals it can develop into a severe form that can result in disability. The understanding of epidemiological and etiopathogenesis aspects of leprosy is needed to understand the basic concept of this disease, then could be led to the idea of further researches.

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