Curr Trop Med Rep (2016) 3:138–143
DOI 10.1007/s40475-016-0095-x

TROPICAL DERMATOLOGY (TL PHUNG, SECTION EDITOR)

Clinical Characteristics and Treatment of Leprosy

Minh Van Hoang[1] · **Duc Van Bui**[1] · **Thuy Linh Phung**[2]

Published online: 18 November 2016

Abstract
Purpose of Review The purpose of this study is to provide an up-to-date review of the clinical presentation, classification system, and treatment of leprosy (also known as Hansen's disease).
Recent Findings Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. Leprosy affects mainly the skin and peripheral nerves with serious clinical complications, including blindness and physical deformities of the hands and feet. Leprosy is a complex microbial disease with a wide spectrum of clinical presentations and severity of disease progression and outcome. Disease classification based on bacterial indicators and the Ridley-Jopling system are standard classification systems for leprosy that enable proper categorization of different types of leprosy for evaluation and treatment purposes. Early disease detection and treatment can significantly impact the prevalence and severity of leprosy. Long term follow-up as well as disability evaluation and prevention are important measures to prevent disease relapse and to achieve a good clinical outcome for patients.
Summary Early disease detection, multidrug therapy, frequent clinical follow-up, and proper management of tissue damage and physical disabilities as a result of peripheral nerve damage are key factors to ensure a good outcome for patients.

This article is part of the Topical Collection on *Tropical Dermatology*

✉ Thuy Linh Phung
tphung@bcm.edu

[1] Department of Dermatology, University of Medicine and Pharmacy of Ho Chi Minh City, Ho Chi Minh City, Vietnam

[2] Department of Pathology and Immunology, Baylor College of Medicine and Texas Children's Hospital, 1102 Bates Avenue, FC 0830.21, Houston, TX 77030, USA

Keywords Leprosy · *Mycobacterium leprae* · Paucibacillary leprosy · Multibacillary leprosy · Erythema nodosum leprosum · Reversal reaction

Introduction

Leprosy (also known as Hansen's disease) is a chronic infectious disease caused by *Mycobacterium leprae*. Leprosy is a worldwide public health issue that affects many parts of world where the disease is endemic. The clinical manifestation and sequela of the disease are primarily due to infection of the skin and peripheral nerves by *M. leprae* leading to blindness and physical deformities. This report describes the classification system of leprosy, its clinical manifestations, and current treatment, as well as the evaluation and prevention of the physical disabilities of the disease.

Clinical Features of Leprosy

Leprosy has a long period of incubation before the clinical manifestation of the disease. The incubation period can range from 3 months to 40 years with the average time of 2 to 5 years [1–3].

Skin Manifestations Skin involvement in leprosy has a wide spectrum of manifestations depending upon the type of leprosy [1, 3, 4]. Skin lesions can be macules, papules, nodules, and plaques. The lesion color can be reddish, copper-colored, or hypopigmented with well-demarcated or indistinct borders. Most lesions do not blanche with local pressure and there is sensory loss with the exception of early macular lesions in lepromatous leprosy type, in which there is normal or even heightened sensation.

Neurologic Manifestations The main neurological defect in leprosy is loss of sensation to temperature, pain, and touch in the affected areas of the skin, such as the hands and feet. The neuropathy primarily involves peripheral nerves, which can be enlarged and easily palpable. The nerves that are commonly affected are the ulna nerve in the medial elbow, posterior tibial nerve in the medial ankle, peroneal nerve, radial nerve, superficial nerves of the neck, and facial nerves [3, 5]. Lesions can be painful due to inflammation of the affected nerves, particularly neuritis involving large myelinated nerves that causes pressure and nerve impingement.

As a consequence of nerve damage in leprosy, there is muscle atrophy and resultant muscle paralysis due to impairment of nerves that innervate the affected muscles [6]. Thenar and hypothenar muscles of the hand can become atrophic due to ulnar and median nerve involvement, and this can lead to hyperextension of the digits and the inability to abduct the thumb of the affected hand (simian hand sign). Loss of the radial nerve and fibular nerve can lead to wrist drop and foot drop, respectively.

The eyes are affected with loss of the ability to close the eyes completely (lagophthalmos) due to impairment of cranial nerves. Other eye conditions in leprosy are uveitis and corneitis. Many of the eye complications occur in advanced lepromatous stage.

Leprosy can involve other tissues and organs, including the nose (rhinitis, epistaxis, and collapsed nostrils), larynx (laryngeal fibrosis resulting in hoarse voice), oral cavity (soft palate ulceration, perforation, and periodontitis), bone and joints (arthritis and osteomyelitis in acral bones and joints that can lead to amputation), epididymitis and orchitis (leading to infertility and gynecomastia) and lymphadenopathy [7].

Classification of Leprosy

Classification Based on Bacterial Indicators The purpose of this classification is to categorize patients into paucibacillary and multibacillary groups in order to provide an appropriate treatment regimen based upon bacteriological findings [8•]. Paucibacillary group does not show the presence of mycobacteria on smears taken from skin lesions and ear lobe. Paucibacillary group has one to five skin lesions as well as one damaged nerve and sensory loss. In contrast, multibacillary group shows the presence of mycobacteria on smears. This group has greater than five skin lesions, more than one damaged nerve and sensory loss.

Ridley-Jopling Classification This classification is based on the integration of clinical, immunologic, bacteriologic, and histopathologic characteristics of the disease [1, 3, 4, 7, 9•]. There are six types of leprosy in the Ridley-Jopling classification: indeterminate leprosy (I), tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB), borderline lepromatous leprosy (BL), and lepromatous leprosy (LL).

Indeterminate Leprosy	This is the initial stage and earliest form of leprosy with non-specific clinical features. The skin lesions are hypopigmented reddish macules with indistinct border and usually appear on the face, trunk, and extensor surface of the extremities. Indeterminate leprosy may heal spontaneously or progress to other types of leprosy.
Tuberculoid leprosy	Skin lesions in TT are hypopigmented, copper-red macules and plaques with distinct border (Fig. 1). The lesions can be atrophic, dry, scaly and have loss of hair. TT lesions are associated with loss of sensation. Peripheral nerves in TT are affected with irregular nerve fiber enlargement. Skin smear for mycobacteria is usually negative, but lepromin test, which is used to detect the type of leprosy a patient has, is strongly positive. TT has a good prognosis with good response to antibacterial treatment. Spontaneous resolution of TT may occur in some cases, but it can progress to other leprosy types.
Borderline Tuberculoid Leprosy	Skin lesions in BT are similar to those in TT with reddish, hypopigmented plaques that have distinct borders. BT lesions show progressive development with more lesion infiltration and the presence of satellite lesions. The lesions can have partial or complete loss of sensation. Multiple peripheral nerves are affected asymmetrically

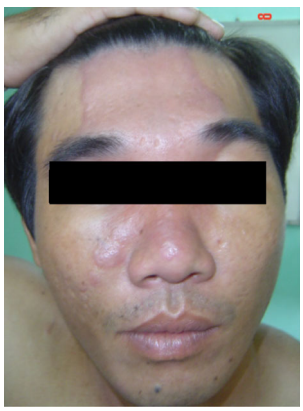

Fig. 1 Tuberculoid leprosy lesions on the face of a patient

with irregular nerve enlargement. Mycobacteria may be detected in skin smears, and lepromin test is usually positive. Skin biopsy of BT lesions shows tuberculoid granulomas in the dermis. BT is associated with type 1 reaction (reversal reaction), and if left untreated, BT can progress to mid-borderline and lepromatous leprosy with associated physical deformities.

Mid-borderline Leprosy: Skin lesions in BB are numerous hypopigmented, reddish color lesions with variable shapes and sizes. Distant satellite lesions are present. BB skin lesions can have a doughnut-shaped appearance with central concavity and irregular outer border and well-defined distinct inner border. The lesions can have partial or complete loss of sensation. Multiple peripheral nerves are affected in BB. Mycobacteria are detected, but the lepromin test is negative. BB has an unfavorable clinical course and is associated with reversal reaction.

Borderline Lepromatous Leprosy: There are numerous lesions, including macules, papules, nodules, and plaques, in BL. The lesions are distributed somewhat symmetrically on both sides of the body. A distinctive sign of BL is the presence of annular plaques with an inverted saucer-shaped appearance of raised central area and sloping edges. The lesions can also be doughnut-shaped with concave center. There is partial or complete loss of sensation in the center of the lesions. Multiple peripheral nerves are affected in BL, and sensory loss can be present in the hands and feet. Mycobacteria are found in skin smears and lepromin test is negative. BL has an unfavorable clinical course and is associated with reversal reaction and erythema nodosum leprosum reaction.

Lepromatous Leprosy: This is the most severe form of leprosy. LL lesions appear as macules initially, and in advanced stage, the skin lesions are numerous and present as macules, papules, nodules, and plaques with reddish color, diffuse infiltration, and indistinct border (Fig. 2). LL skin lesions are raised in the center and slope off gradually in the periphery.

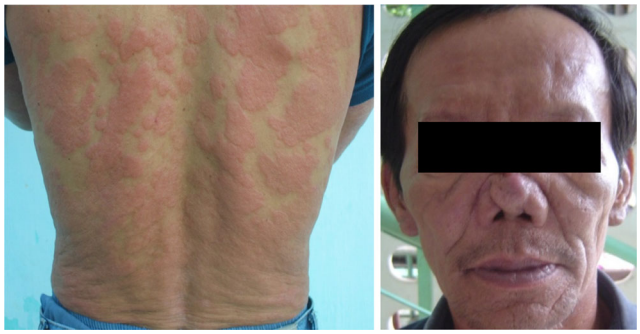

Fig. 2 (*Left*) lepromatous leprosy lesions on the back, and (*right*) collapsed nostrils and loss of eyebrows in a patient with lepromatous leprosy

The lesions appear symmetrically throughout the body, but they appear more frequently on the face, ear lobes, hands, and feet. Sensory loss may not occur in early lesions. Sometimes these lesions even have hyperesthesia or increased sensation. Sensory loss can occur, especially in the hands, forearms, and feet in a glove-and-stocking pattern. As the disease progresses to a more severe stage, numerous cutaneous nodules with marked infiltration are present on the face and the facial skin can appear in folds, giving the appearance of "leonine faces." The eyebrows and eyelashes may be lost, and other systemic symptoms, such as epistaxis, collapsed nostrils, and orchitis, may appear. Mycobacteria are found in skin smears and lepromin test is usually negative. LL has an unfavorable clinical course and is associated with reversal reaction and erythema nodosum leprosum reaction. Skin biopsy of LL shows foam cells (lepra cells) with vacuolated cytoplasm containing numerous *M. leprae* on acid-fast bacilli stains.

Special Types of Leprosy

Pure neural leprosy: This is a type of paucibacillary leprosy is characterized by only neural impairment without skin involvement [10–12]. It occurs more often in men than women with a 3:1 male to female ratio. Pure neural leprosy (PNL) is more frequently seen in India than in other parts of the world. Enlargement of the

	ulna nerve is commonly seen in PNL. Other clinical features of PNL include sensory loss, skin atrophy, and paralysis. Mycobacterial smears are usually negative, and lepromin test is weakly positive.
Lucio leprosy	This is a form of lepromatous leprosy that is common in Mexico and South America [13–15]. Lucio leprosy is characterized by diffuse cutaneous infiltrations with hair loss (mainly in the eyebrows and eyelashes) and widespread sensory loss. Mycobacterial smears are often strongly positive.
Histoid leprosy	This is a rare variant of leprosy with pathological findings of dense bundles of histiocytes containing *M. leprae* arranged in a storiform pattern [16]. Clinically, histoid leprosy lesions are smooth, reddish firm papules and nodules that mimic fibromatous disorders. Histoid leprosy occurs in patients with multibacillary leprosy and a high load of bacilli who have developed bacterial resistance to dapsone treatment.

Immune Reactions to Leprosy

Inflammatory immune reactions to *M. leprae* infection are classified as type 1 and type 2 lepra reactions. Type 1 lepra reaction, or better known as reversal reaction, can occur in both paucibacillary leprosy and multibacillary leprosy. Reversal reaction is a delayed hypersensitivity reaction caused by increased activity of the immune system, in particular cell-mediated immune response, to antigenic determinants in leprosy bacilli [17]. Clinical features of reversal reaction include increased severity of existing skin lesions, development of new skin lesions, and neuritis involving peripheral nerves, which can appear during the first few months of drug therapy for leprosy (Fig. 3).

Type 2 lepra reaction, also known as erythema nodosum leprosum (ENL), occurs in patients with lepromatous leprosy and a heavy bacterial burden [18]. ENL arises after several months of drug therapy, but it can also develop in untreated patients. ENL is caused by humoral-mediated immunity to antigenic determinants of *M. leprae*, and the circulation and deposition of immune complexes in various tissues, compliment fixation and subsequent cellular destruction. Clinical features of ENL include malaise, fever, painful peripheral nerve lesions, and painful and indurated skin nodules (Fig. 4). Hepatomegaly and splenomegaly occasionally occur in ENL.

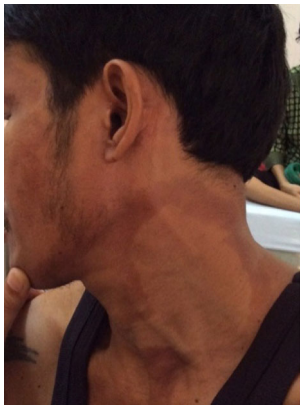

Fig. 3 Reversal reaction with associated hypertrophy of a superficial neck nerve in a patient with borderline leprosy

Treatment of Leprosy

Current treatment regimen for leprosy involves multi-drug therapy combined with physical therapy for patients with physical disabilities from the disease. A first- line therapeutic drug for leprosy is dapsone [19, 20•]. It is low cost and easy to use with good absorption in the gastrointestinal tract. Typical dosage for adult patients is 1–2 mg/kg/day. Side effects of dapsone include hemolytic anemia, headache, methemoglobinemia, gastrointestinal disorders, hepatitis, and neuropathy. However, these side effects are infrequent at the standard drug dose.

Rifampicin and clofazimine are other drugs for leprosy treatment [21]. Rifampicin has strong bactericidal activity, and at a dosage of 600–1500 mg per day, rifampicin can kill over 90 % of *M. leprae*. A typical dosage in adult patients is 5–10 mg/kg/day. Side effects of rifampicin include skin pruritus and rash, influenza-like symptoms, purpura, and hepatitis. Fortunately, rifampicin has few side effects at the clinically indicated treatment dose.

Clofazimine is weakly bactericidal. It is first deposited in adipose tissues and the reticuloendothelial system with drug distribution in the skin about 4–6 weeks after the initial dose. Drug dosage is 50–100 mg per day. Side effects of

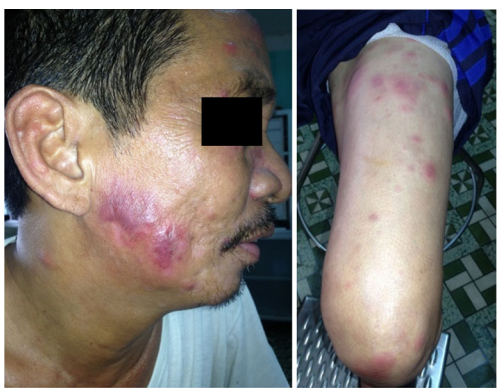

Fig. 4 Erythema nodosum leprosum lesions in a patient with borderline lepromatous patient

clofazimine include brown skin discoloration, xerosis, acneiform eruptions, and occasional gastrointestinal symptoms [19, 22]. Contraindications for use of clofazimine are hepatitis and chronic diarrhea. Rifampicin, clofazimine, and dapsone are combined as multidrug therapy to treat multibacillary leprosy.

Other alternative drugs are pefloxacin, ofloxacin, clarithromycin, and minocycline for lepromatous leprosy [23–25]. Ofloxacin in particular has a killing efficacy of 99 % of *M. leprae* at 400 mg per day. Minocycline can be used to treat peripheral neuritis in leprosy [26].

Bacterial Drug Resistance This is a major obstacle in leprosy treatment. Drug resistance should be suspected if a patient shows no improvement or if there is development of new active skin lesions even when the patient follows a prescribed drug regimen. A large number of multibacillary patients have resistance to standard therapy for leprosy, such as dapsone [27]. Resistance to dapsone is particularly high in patients who do not take the drug as prescribed. There are also some reported cases of bacterial resistance to rifampicin.

Long-Term Follow-Up After Treatment Continued follow-up after completion of medical treatment for leprosy is necessary in order to monitor for disease relapse. Should relapse occur as evident by new skin lesions, fever, pain, muscle weakness, and peripheral neuropathy, patients should be requested to return for medical evaluation immediately. Disease relapse in multibacillary leprosy can be readily detected by laboratory tests and skin biopsy to evaluate for *M. leprae*. However, relapse in paucibacillary patients is somewhat more difficult to determine because it is hard to distinguish relapse from type 1 reversal reaction. Paucibacillary patients should have a clinical examination performed every year for 2 years as part of their follow-up. Multibacillary patients should have clinical examination performed every year for 3 to 5 years. Patients with disease relapse should be treated with multidrug therapy and followed carefully in case there is a need to switch to a different anti-bacterial regimen.

Disability Evaluation and Prevention Physical disability caused by skin and peripheral nerve damages as a result of *M. leprae* infection can be devastating to patients. The disability classification scheme for leprosy by the World Health Organization (WHO) is a simple and easy-to-use system (Table 1) [28, 29].

Effective treatment for leprosy combines medical treatment with physiotherapy to prevent or limit disabilities from the physical deformities caused by the disease. Physiotherapy includes exercises, wax baths, massage, and well-fitting shoes. In addition, patient education is important in order for patients to be aware of what should be done in order to prevent or limit hand and foot deformities as a result of sensory loss. For example, patients should not place their hands close to an open flame or directly touch hot objects that can cause skin burn, walk barefoot, or wear ill-fitting shoes. Patients should keep their skin well hydrated and moisturized to prevent dry and cracked skin that can serve as a portal of skin infection. They should perform self-examination for any skin injury and treat the injury immediately to prevent infection.

Steps to prevent eye injuries are important to prevent lagophthalmos and loss of corneal reflex due to facial nerve and optic nerve damages that can lead to infection and blindness. Protective measures for the eyes include washing the face with clean water and clean towel, avoid rubbing the eyes, and wearing eye protection if they are in a dusty place where dust particles can get into the eyes, or if they are involved in activities that require eye protection.

Measures to prevent leprosy are based on early detection, accurate diagnosis, timely treatment, physical therapy, and public health education. Early disease detection is important in order to evaluate and treat affected individuals rapidly to limit the spread of disease in the general population and allow for early therapeutic intervention. In addition, it is important to provide health education to healthcare providers and the public about leprosy in order to raise awareness about the early signs and symptoms of the disease as well as reducing discrimination and stigma against persons with leprosy. It is equally important to integrate leprosy elimination program with primary health care network in the community to promote health education activities and provide specific training to health workers about leprosy in order to detect the disease early and improve clinical outcome.

Table 1 World Health Organization (WHO) disability classification for leprosy

Grade	Hands[a]	Feet[a]	Eyes[b]
0	- No anesthesia - No visible deformity or damage	- No anesthesia - No visible deformity or damage	- No eye problems and no evidence of visual impairment
1	- Anesthesia is present but no visible deformity or damage	- Anesthesia is present but no visible deformity or damage	- Eye problems are present but no significant visual impairment
2	- Visible deformity is present	- Visible deformity is present	- Severe visual impairment is present (e.g., patient is not able to count his fingers at a 6-meter distance)

[a] Each hand and foot should be evaluated and graded separately. Hand and foot damages include skin ulceration, stiffness, and shortening of the digits, or loss of part or all of the hand or foot

[b] Eye problems include corneal anesthesia, lagophthalmos, and corneitis. Each eye should be evaluated and graded separately

Conclusions

In summary, leprosy is a complex microbial disease with a wide spectrum of clinical presentations and severity in terms of disease progression and outcome. Early disease detection and treatment are the best approaches for a favorable clinical outcome for patients. Multidrug therapy, frequent clinical follow-up, and proper management of tissue damage and physical disabilities as a result of peripheral nerve damage are key factors to ensure a good outcome for patients.

Acknowledgments We would like to thank Mahmoud Bokhary, MD, for his valuable assistance with the bibliography of this article.

Compliance with Ethical Standards

Conflict of Interest Minh Van Hoang, Duc Van Bui, and Thuy Linh Phung declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Yawalkar SJ, editor. Leprosy for medical practitioners and paramedical workers. 8th revised ed. Basle, Swizerland: Novartis Foundation for Sustainable Development; 2009. p. 152.
2. Klaus Wolff RAJ, Saavedra AP, editors. Fitzpatrick's color atlas and synopsis of clinical dermatology. 7th edition. Color atlas & synopsis of clinical dermatology (Fitzpatrick). New York: McGraw-Hill Medical; 2013. p. 960.
3. Talhari C, Talhari S, Penna GO. Clinical aspects of leprosy. Clin Dermatol. 2015;33(1):26–37.
4. Odom RB, James W, Berger TG, editors. Berger Andrew's diseases of the skin. Clinical Dermatology: USA; 2000. p. 713.
5. Butlin CR, Saunderson P. Children with leprosy. Lepr Rev. 2014;85(2):69–73.
6. Talwar BH, Nirmala C, Somnath L. Nerve FNAC in diagnosing Hansen's disease: a prospective study. J Evol Med Dent Sci. 2016;5(15):711–6.
7. Grossetete G et al. Leprosy. Developmental modalities. Rev Prat. 1992;42(5):606–12.
8.• Parkash O. Classification of leprosy into multibacillary and paucibacillary groups: an analysis. FEMS Immunol Med Microbiol. 2009;55(1):1–5. **This paper reviews the classification of leprosy based on bacterial burden**.
9.• Features of the Ridley-Jopling classification. Int J Lepr Other Mycobact Dis. 1979;47(4): 611–2. **This publication describes the widely accepted Ridley-Jopling classification of leprosy based on a combination of clinical, immunologic, bacteriologic and histopathologic characteristics of the disease**.
10. Pardal-Fernandez JM et al. Pure neural leprosy. Diagnostic aspects of a clinical case. Rev Neurol. 2016;63(6):257–61.
11. Jardim MR et al. Criteria for diagnosis of pure neural leprosy. J Neurol. 2003;250(7):806–9.
12. Bezerra Da Cunha FM et al. Pure neural leprosy: diagnostic value of the polymerase chain reaction. Muscle Nerve. 2006;33(3):409–14.
13. Saoji V, Salodkar A. Lucio leprosy with lucio phenomenon. Indian J Lepr. 2001;73(3):267–72.
14. Kim JY, Chung KY, Kim WJ, Jung SY. Lucio phenomenon in non-endemic area of Northeast Asia. J Eur Acad Dermatol Venereol. 2016. doi:10.1111/jdv.13920.
15. Kaur C, Thami GP, Mohan H. Lucio phenomenon and Lucio leprosy. Clin Exp Dermatol. 2005;30(5):525–7.
16. Gupta SK. Histoid leprosy: review of the literature. Int J Dermatol. 2015;54(11):1283–8.
17. Walker SL, Lockwood DN. Leprosy type 1 (reversal) reactions and their management. Lepr Rev. 2008;79(4):372–86.
18. Cuevas J et al. Erythema nodosum leprosum: reactional leprosy. Semin Cutan Med Surg. 2007;26(2):126–30.
19. Kar HK, Gupta R. Treatment of leprosy. Clin Dermatol. 2015;33(1):55–65.
20.• Shen J et al. Six years' follow-up of multibacillary leprosy patients treated with uniform multi-drug therapy in China. Int J Dermatol. 2015;54(3):315–8. **This paper describes the efficacy and importance of multi-drug therapy for multibacillary leprosy**.
21. Legendre DP, Muzny CA, Swiatlo E. Hansen's disease (Leprosy): current and future pharmacotherapy and treatment of disease-related immunologic reactions. Pharmacotherapy. 2012;32(1):27–37.
22. Maia MV, Cunha Mda G, Cunha CS. Adverse effects of alternative therapy (minocycline, ofloxacin, and clofazimine) in multibacillary leprosy patients in a recognized health care unit in Manaus, Amazonas, Brazil. An Bras Dermatol. 2013;88(2):205–10.
23. Fajardo Jr TT et al. Minocycline in lepromatous leprosy. Int J Lepr Other Mycobact Dis. 1995;63(1):8–17.
24. Grosset JH. Newer drugs in leprosy. Int J Lepr Other Mycobact Dis. 2001;69(2 Suppl):S14–8.
25. Setia MS et al. Is there a role for rifampicin, ofloxacin and minocycline (ROM) therapy in the treatment of leprosy? Systematic review and meta-analysis. Trop Med Int Health. 2011;16(12):1541–51.
26. Narang T, Arshdeep, Dogra S. Minocycline in leprosy patients with recent onset clinical nerve function impairment. Dermatol Ther. 2016. doi:10.1111/dth.12404.
27. Matsuoka M. Global surveillance system to monitor the development of drug resistance in *Mycobacterium leprae*. Research and Reports in Tropical Medicine. 2015;6:75–83.
28. Alberts CJ et al. Potential effect of the World Health Organization's 2011–2015 global leprosy strategy on the prevalence of grade 2 disability: a trend analysis. Bull World Health Organ. 2011;89(7):487–95.
29. Thappa DM. Disability grading in leprosy: current status. Indian J Lepr. 1994;66(3):299–306.