INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

CONTEMPORARY APPROACHES USED IN LEPROSY

NischalTyagi and VineetaTripathi*

I.T.S Paramedical College, Meerut Road, Ghaziabad, Uttar Pradesh, India.

ABSTRACT

Leprosy (Hansen's disease) is a slowly developing, progressive disease caused by *Mycobacterium lepraeor M. lepromatosis* bacteria with the symptoms of nerve damage, skin lesions and visual impairment. India is considered the point of origin of leprosy with skeletal evidence of the disease dating to 2000 B.C. at current time leprosy affects approximately a part of a million people throughout the world, with majority of these cases being reported from India. For increasing the public awareness about leprosy World Leprosy Day is celebrated on 30 January every year. The WHO introduced a multidrug regimen (rifampicin, dapsone and clofazimine) in 1981 and recently recommended single drug regimen in case of leprosy treatment. This therapy has proved to be the most reliable and useful method of treating leprosy.

Keywords: Clofazimine, Dapsone demyelination, Rifampicin.

INTRODUCTION

Leprosy is an ancient infectious disease dating back as early as 1550 B.C, has played a significant role in the mankind as a feared, misunderstood and disfiguring disease. The causative agent of leprosy, *Mycobacterium leprae* is discovered by Dr.Armauer Hansen in 1873. It is an acid-fast bacillus, major human pathogen and grows best in cooler tissues (skin, peripheral nerve, anterior chamber of eyes, upper respiratory tract, and testes).[1]Most people are resistant to the *M. leprae* infection and do not develop clinical leprosy. Only some individuals develop the different phases of the clinical leprosy and progress to systemic disease, depending upon the host response the incubation period of leprosy is between to range from 9 months to 20 years. The main clinical features of leprosy are a variety of lesions and peripheral nerve damage, visual impairment, which leads to anaesthesia and paralysis.[2]

EPIDEMIOLOGY

Leprosyoccurs in both tropical and subtropical temperate climates. It is an important public health problem, especially in Africa, and South America, India,Brazil, Indonesia, Bangladesh, Nepal, Angola, China, Madagascar, Mozambique, Nigeria, the Philippines, and the united republic of Tanzania.[3]Management of leprosy has enhancedconsiderably due to national and sub national campaigns in most prevalent countries. incorporationof primary leprosy services with the existing general health services has made its diagnosis and treatment easy but still it is a seriousdisease.In year 2010, 211,903 cases of leprosy were reported by World Health Organization (WHO) in 141 countries.The global recorded prevalence of leprosy in the beginning of 2011 was 192,246 cases.The number of new cases accountedworldwide in 2012 was 232. National leprosy programmes for 2011 – 2015 now focuses more upon underserved populations and remote areas to improve access and treatment. National programmes increasingly enhance case holding, contact tracing, observing, referring and record maintenance.[4]

PATHOPHYSIOLOGY

M.leprae, an acid- fast bacillus is a major human pathogen and known for their notoriously slow growth.Schwann cellsare major target of *M.leprae* leading to injury of nerve, demyelination and subsequent disability.[5, 6]It has been shown that *M.leprae*can attack Schwann cells by a specific lamininbinding protein of 21 kDa in addition to PGL-1, a major unique glycoconjugate on the *M.leprae*surface, binds laminin-2, which explains the weakness of the bacterium for peripheral nerves.[7,8]The identification of the *M.leprae*-targeted Schwann cells receptor, dystroglycan (DG), plays a major role for thismolecule in early nerve degeneration.[9]The direct bacterial ligation of *M.leprae* to neuregulin receptor induced demyelination, ErbB2 and Erk1/2 activation, and subsequent MAP kinase signalling and proliferation.[10]Phagocytosis of *M. leprae*by monocyte-derived macrophages can be mediated by complement receptors CR1 (CD35), CR3 (CD11b/CD18),and CR4 (CD11c/CD18).[11, 12]

Incubation period

Determining the incubation period in leprosy is difficult because of the lack of adequate immunological tools and slow onset of the disease. The least incubation period reported is as short as a few weeks. The maximum incubation period is reported is as long as 30 years, or more. It is generally believed that the average incubation period is between three and ten years.[13,14]

Mode of Transmission

The mode of transmission is not well identified. Although two main routes from human body often describe are the skin and nasal mucosa. Nasal discharge of the affected patient has shown large number of acid fast bacteria. It is not transmitted by sexual contact. Experimental transmission of leprosy is done via aerosols in mice.[15]

Classification of leprosy

There are two systems used to classify leprosy patients, first one is proposed in 1966 Ridley-jopling classification is most comprehensive and accurate and uses clinical and histopathological features and the bacterial index to identify the five different types of leprosy.Second one is the WHO classification, based upon the number of skin lesions.[16]

1. Ridley-jopling classification-

- Tuberculoid polar leprosy (TT)
- Borderline tuberculoid(BT)
- Mid-borderline(BB)
- Borderline lepromatous(BL)
- Lepromatous polar leprosy (LL)

Tuberculoid polar leprosy(TT) –In TT there is well developed cell-mediated immunity and has very low bacillaryload. TT may be purely neural, with pain or swelling of the affected nerves**,** followed by anaesthesia and likely to cause muscle weakness and wasting. On the other hand skin lesionsmay also appear with or without indication of nerve involvement. These are single or few in number andusually present as hypopigmented, erythematous coppery patches, with awell defined, but irregular and often slightly raised edges. The lesions are non-sweating,have decreased hair and sensation. Diagnosis depends on clinical examination and biopsy, as smears are usually negative.

Symptoms

Early symptoms can include one or more light or slightly red patches of skin that appear on the trunk or extremities. This may be associated with a decrease in light-touch sensation in the area of the rash. Other tuberculoid leprosy symptoms can include:

- Severe pain
- Muscle weakness, especially in the hands and feet
- Skin stiffness and dryness
- Loss of fingers and toes
- Eye problems, which lead to blindness
- Enlarged nerves, especially those around the elbow (ulnar nerve) and knee (peroneal nerve).

Borderline tuberculoid (BT)

Borderline tuberculoid (BT) lie in the middle of the polar TT to LL spectrum. This form is seen in those people with limited or variable resistance to *M. leprae*. Skin and nerve involvement is commonly seen, with only rare involvement of other structures.

Symptoms

- Lesion like tuberculoid but small
- Less nerve enlargement
- Revert to tuberculoid

Mid- borderline (BB)

BB leprosy is the immunologic midpoint in the clinical spectrum of the granulomatous disease. It is the most unstable and uncommon form of leprosy.

Symptoms
- Reddish plaques
- Moderate numbness
- Swollen lymph glands

Borderline lepromatous (BL)
BLis a skin condition with numerousskin lesions.

Symptoms
- Many lesions with flat lesions
- Raised bumps,Plaques, and nodules
- Sometimes numb

Lepromatous leprosy (LL)-Lepromatous leprosy is less common but is a more severe and immobilizing disease. There is loss ofleprosy-specific mediated immunity with no control on multiplication and spread of bacilli.

Early symptoms include:
- Skin lesions
- Nasal symptoms

Other symptoms include:
- Thinning of eyebrows and eyelashes
- Thickened skin on face
- Laryngitis
- Collapsing of the nose
- Swelling of the lymph nodes in the groin and armpits
- Scarring of the testes that leads to infertility
- Enlargement of male breasts (gynecomastia)[15]

2. WHO Classification
WHO classification is used ever since 1997 and is based on the evaluation of the number of skin lesions and was intended to simplify and helpin diagnosis of leprosy.
Two broad categories are:
- **Paucibacillary leprosy (PBL)**

PBL includes TT, BT, I (indeterminate) and polyneuritic. PBL is further classify between SLPB (Single Lesion Paucibacillary Leprosy) and PB.
- **Multibacillary leprosy (MBL)**

These includes BB, BL and LL. Table no.-1[16, 17]

Diagnosis

A complete history and physical examination in addition to laboratory are essential to diagnosis of leprosy. The main components of the clinical assessment are:
- History
- Skin examination
- Nerve palpation
- Nerve function impairment (NFI)
- Eye examination
- Deformity, disability and psychological assessment
- Nerve damage
- Diagnostic tests

1) History
The patient can be taken for the enquiry about the presence and duration of lesions, nerve pain, numbness, tingling, weakness, ulcers, injuries, eye pain and worsening vision.

2) Skin examination
Skin surface examined carefully for lesions that can include macules, papules, plaques, nodules, urticaria-like lesions and smooth infiltration. Patches may appear coppery on dark skin and pink on fair skin. Also examine the loss of sensation, hair, pigmentation and sweating. Natural sunlight is best for the examination of the skin.

3) Nerve palpation
The mostly affected nerves are the ulnar, median, radial cutaneous, common peroneal(lateral popliteal) and posterior tibial nerves, the sural nerve, the 5^{th} and 7^{th} cranial nerves, and the greater auricularnerve. Patients may also present with the limb deformities and chronic ulceration and scarring on hands and feet, resultant trauma to area with loss of sensation. Patients may also suffer from the neuropathic joint pain, traumatised by repeated injury to a joint with no protective sensation. *M .leprae* prefers to multiply in vivo at a temperature 27-30^{o}c.

4) Nerve function impairment (NFI)
NFIis a clinically detectable loss of motor, sensory or autonomic peripheral nerve function. *M .leprae* is the only bacterial agent known to specifically infect peripheral nerves. NFI includes silent neuropathy and type1 and type 2 reactions.

5) Deformity, disability, psychological assessment

Abnormality or disability is an important part of the initial clinical assessment.Deformities can result from infection, relapse or Type 1 and Type 2 immune reactions and together may lead to irreversible nerve damage. This further may impact upon the patient's psychological and social wellbeing, leading to anxiety or depression that is caused by the stigmatised view of leprosy in many civilizations.

6) Eye examination

The sign and symptoms which can be observed into the leprosy patient arespontaneous blinking, test with cotton wool if less than 3 blinks per minute, moderate eye closure with effort, and against resistance exposure keratitis (lower half of cornea dry, scarred), eye pain/ache , photophobia, tenderness, tearing, redness (perilimbal) small, poorly reactive, ovoid pupil dull cornea reduced visual acuity, deep red sclera patch can be produced including other complications like madarosis(loss of eyebrows and lashes), corneal hypoesthesia (loss of corneal sensation to cotton wool), lagophthalmos(weakness or paralysis of orbicularis oculi(muscle leading to lid gap), iridocyclitis (inflammation of iris and ciliary body, scleritis (inflammation of sclera near the cornea), dacrocystitis(inflammation of lacrimal sac) and cataract.[18,19]

7) Histological examination

The skin lesion and nerve are examined for the typical histological changes and the presence of acid-fast bacilli is required for the positive diagnosis of leprosy. All cases of leprosy should initially be confirmed histologically as tagging a person with leprosybears with it direct social and medical implication.

- **Slit skin smear to detect acid**-fast bacilli from lesion skin provides a fast confirmation of multibacillary leprosy. It is also useful as a sign of improvement in patients with multibacillary leprosy undergoing treatment. The test requires trained personnel to obtain reliable results. It is cheap but generally unavailable. While a positive test confirms further diagnosis of leprosy, a negative test does not completely exclude it. The indices reported are Bacterial Index (BI), which is the measure of the total number of bacilli and Morphological Index (MI) which measures the percentage of viable bacilli in the specimen.
- **Lepromin test**- is an intradermal test with autoclaved Mycobacterium leprae antigen. It is a guide to the cell- mediated immunity (Mitsuda and Fernandes reactions) of the patient against leprosy. It is not useful as a confirmatory tool in diagnosis of leprosy but a negative test can be useful to exclude leprosy in patients with peripheral neuropathy.
- **Phenolic glycolipid-1 (PGL-1)**-IgM antibody detection is of limited clinical use as it is positive in 100% of multibacillary leprosy but in only 21 % in paucibacillary leprosy and 14% in household contacts. [20]

Reactions in Leprosy

Wide spectrum of disease caused by *M.lepra*einfection, the management of leprosy is furthercomplicated by the development of immune reactions(types I and II), which may occur at any time before, during,or after treatment. These reactions are associatedwith neuritis and painful skin lesions, which may be asignificant source of morbidity separate from the consequencesof bacterial replication. Reactions are classifiedas type I (reversal reaction) or type II (Erythema NodosumLeprosum), which have different mechanisms, risk factorsand treatments.[21, 22]

Type I reaction

This is also known as reversal reaction, occuramong the borderline subtype.[23] The symptoms includeinflammation and edema of skin lesions as well as neuritis.[24]This reaction can occur at any time, but generally occurs after MDT (Multidrug treatment). [25, 26]The reactions representan acute increase in immune function, which leads to aninflammatory response in affected areas.[24]Histologically,biopsies from active reactions show edema, increasedvascularity, and lymphocytic infiltration, all of whichcause swelling and compression of nerves, eventuallyleading to fibrosis.[27] Whereas this upgraded immune responsemay be good for bacillary clearance, the resultingneuritis and edema may cause permanent disability if nottreated. Treatment of the reaction includes controllingthe acute inflammation to ease pain and reverse eye andnerve pain.[23]

Type II reaction

This reaction isalso known as erythema nodosumleprosum (ENL) and occur in patients of either BL or LLsubtype.[23, 31, 28, 29]These reactions are systemic affectingmany organ systems. The onset is acute but symptomsmay become chronic or recurrent.Symptoms of

ENLare diverse but most commonly include fever and painfulred nodules or papules that commonly occur on the faceand extensor surfaces. Deep lesions may progress topanniculitis, whereas a less common subtype of bullousENL may actually ulcerate. Subcutaneous involvementmay lead to tethering and fixation of joints. The commonorgan system effects include uveitis, neuritis, arthritis,dactylitis, lymphadenitis, orchitis and nephritis. The proposedmechanism of action of these reactions is formationof antigen-antibody immune complexes combined withcomplement that are deposited in skin, blood vessel walls,nerves, and other organs leading to acute inflammation.[30]However, these immune complexes have not been identifiedin biopsies of the ENL lesions.[24] Treatment of type II reactions isimmunosuppressant with high-dose of corticosteroids. Table no.-2[23]

Prevention and Treatment

Prevention

The strategy aims at preventing exposure to the disease. It can be approached through improvingeducation of health staff, environmental factors and by immunoprophylaxis of babies with BCG.

BacilliCalmette-Guérin (BCG) vaccine at birth

BCG vaccine has protective effect in leprosy, however the protection is average. Protection is found better in multibacillary leprosy compared with paucibacillaryforms of the diseases.It has also been revealed that it offers reduced protection with advancing age. The protective effect isgreater in women compared with men according to a experimental trial.[31]

Treatment

Clinical management of leprosy has been based on multidrug therapysince 1982.[16]Several drugs are used in combination of multidrug treatment such as rifampicin, dapsone and clofazimine, but they are not used alone as mono therapy.The first WHO MDT guidelineswere accepted in 1982 which included supervised monthly rifampicin and clofazimine and daily unsupervised administration of dapsone and clofazimine for 2 years for MB leprosy.[32]Though in 1998, WHO condensed the standard course of MDT treatment of MB disease to 1 year, and also eliminated the requirement for any bacteriological estimation. Factors that should be considered in deciding asuitable regimen are the type of leprosy (PB or MB), previous treatment if any and drug resistance. Clinicians may use their own judgment sometimes to modify the standard WHO treatment regimens according to the situation of each patient.Table no.-3,4,5[33]

- **Rifampicin**

1. It is bactericidal to *M. leprae*
2. Killed *M.leprae* in 3-7 days
3. Not effective alone
4. Should not be given in case of hepatic and renal dysfunction

- **Dapsone**

1. Used in multidrug therapy
2. Should not be used patients with severe anaemia

- **Clofazimine**

1. It is orally active
2. It has anti- inflammatory property
3. The major disadvantage of clofazimine is discoloration of skin.[32]

Drug resistant leprosy

Long-term monotherapy with dapsoneresults in poor compliance and eventuallyleads to the dapsone-resistant leprosy which further results in treatment failure and resistance levels are reported to be as high as 40% in various areas of the world.Rifampinis anotherpotent antileprosy drug but its monotherapyor in combination with dapsone for the treatment of dapsone-resistant leprosy led to the quick development of rifampin-resistant organisms.[34,35]To overpower the difficulty of drug-resistant *M.leprae*and to improve treatment efficacy, the World Health Organization suggested multidrug therapy regimen for successful treatment of leprosy in year 1981.For treating drug resistant leprosy (clofazimine 50 mg, Ofloxacin 400 mg, and minocycline 100 mg daily for 6 months) even if dapsone resistance is detected; but if rifampin-resistant M. leprae are present, or both dapsone and rifampin resistance are present, then this same combination of drugs (clofazimine 50 mg, Ofloxacin 400 mg, and minocycline 100 mg daily) should be continued for another 18 months or a total of 24 months.[36]

Current treatments

Antimicrobial drugs

Moxifloxacin, linezolid were tested in micefootpads for bactericidal action against *M. leprae*. They were assessed alone and also in combination with the rifamycins – rifampicin (rifampin) and rifapentine, to simulate a MDT

regimen. All three were found bactericidal against fast multiplying *M. leprae*.Telithromycin is a ketolide; a new class of macrolide antibiotics shows strong activity againstmycobacteria and exhibits considerable bactericidal activity against *M. leprae.*[37, 38, 39]

Vitamin D

It has been recently found that how vitamin D is involved in adaptive T-cell activation. ActivatedT-cells further transform into two types of immune cell. They either become killer cells that attack and destroy all cells carrying traces of a foreign pathogen, or they become T helper type 1 cells (Th1) that help the immune system in obtaining "memory." The Th1 cells send signals to the immune system and pass the knowledge regarding the pathogen so that the immune system can recognize and remember it for the next time.[31]With this finding, the researchers recognized a potential therapeutic approach that doesn't rely on administering drugs toxic to *M. leprae*, but rather administering anti-hsa mir-21 to help counter the overexpression of hsa-mir-21 induced by *M. leprae*, in combination with vitamin D supplementation.This combination given in a proper dose can promote a strong adaptive immune response to check or even cure the *M. leprae* infection.[40]

Table 1: Classification of Leprosy

Clinical Classification	SLPB	PBL	MBL
No. of Skin Lesions	Only 1 lesion	2 – 5 lesions	6 or more
Skin Smears	Negative at all sites	Negative at all sites	Positive at all sites
Distribution	-	Asymmatrical distribution	More symmatrical distribution
Loss of Sensation	Definite loss of sensation	Definite loss of sensation	Extensive sensation loss
Nerve damage	No nerve trunk involvment	Only one nerve trunk	Many nerve trunks
Ridley – Jopling Correlation	I, TT, some BT	TT, most BT	Some BT, BB, BL and LL

Table 2: Comparison between the type 1 and type 2 reaction

	Type 1	Type 2
Classification	BT, BB, BL	LL (Occasionally BB, BL)
Immunology	Changing cell mediated immunity	Immune complex deposition, elevated TNF alpha level, dysfunctional cell mediated immunity
Classification change	Upgrading towards TT	No changes
Timing	First month of MDT	May be years after treatment
Recurrent	Usually not	Often
Duration	Several months	Two weeks
Sites of inflammation	Nerves, skin lesions	Skin nodules, iris, testes, joints, nerves

Table 3: WHO recommended treatment regimens
Six months regimens for paucibacillary leprosy

	Dapsone	Rifampicin
Adults 50 -70 Kg	100 mg given daily	600 mg given once a month
Child 10 -14 years	50 mg given daily	450 mg once a month

Table 4: Twelve months regimens for multibacillary leprosy

	Dapsone	Rifampicin	Clofazimine
Adults 50 -70 Kg	100 mg given daily	600 mg given once a month	50 mg given daily and 300 mg given once a month
Child 10 -14 years	50 mg given daily	450 mg once a month	50 mg given every other day and a50 mg given once a month

Table 5: Single lesion paucibacillary leprosy (SLPB)

	Rifampicin	Ofloxacin	Minocycline
Adults 50 -70 Kg	600 mg	400 mg	100 mg
Child 5 – 14 years	300 mg	200 mg	50 mg

CONCLUSION

The disease has been around since ancient times, often surrounded by shocking, negative stigmas and tales of leprosy patients being shunned as outcasts. Successful treatment of leprosy have affected, and panicked, people on every continent. Introduction of multi-drug therapy (MDT) into the National Leprosy Eradication Program (NLEP) of India has brought a refuse in both the burden of the disease and the detection of new cases in the country. In spite of this success, MDT has had many problems like remarkable relapse rate, non-adherence to the MDT and drug resistance associated with it. But at the present time, there is no new MDT regimen, which could solve all these problems. The current situation suggests that we should look for alternative solutions in the treatment of leprosy.

ACKNOWLEDGEMENT

I thank ITS Paramedical College for providing me with all the facilities required in development of this review article.

REFERENCES

1. Rees RJW, McDougall AC,Airborne Infection with *Mycobacterium Lepra*ein Mice,J. FMedMicrobiol. 1977;10: 63-68.
2. Fine PEM, Sterne JAC,Ponnighaus JM, Bliss L, Saul J, Chihana A, Munthali M, Warndorff DK, Household and Dwelling Contact as Risk Factors for Leprosy in Northern Malawi,Am J Epid.1997;146: 91-102.
3. Lira KB, Leite JJG, Maia DCB, Freitas RMF, Feijao AR,Knowledge of the patients regarding leprosy and adherence to treatment,Braz J Infect Dis. 2012; 16:472–475.
4. Begg K, Roche P, Owen R, Liu C, Kaczmarek M, Hii A, Australia's notifiable diseases status, CDI. 2008; 32:139-207.
5. Rastogi N, Legrand E, Sola C, The Mycobacteria: an introduction to nomenclature and pathogenesis, OIE Revue Scientifiqueet Technique. 2001;20: 21-54.
6. Gutierrez MC, Supply P.Brosch R, Pathogenomics of mycobacteria,Genome Dynamics. 2009; 6: 198 -210.
7. Marques MAM, Antonio VL, Sarno EN, Brennan PJ, Pessolani PCV, Binding of alpha 2- laminins by pathogenic and non- pathogenic mycobacteria and adherence to Schwann cells,J med Microbiology. 2001; 50: 23-28.
8. Zanazzi G, Timpl R, Role of the cell wall phenolic glycolipid – 1 in the peripheral nerve predilection of Mycobacterium leprae, Cell. 2000; 103: 511- 524.
9. Rambukkana A, Yamada H, Zanazzi G,Role of *α*- dystroglycan as a Schwann cell receptor for *Mycobacteriumleprae*, Science. 1998; 282: 2076–2079.
10. Tapinos N, Ohnishi M, Rambukkana A,ErbB2 receptor tyrosine kinase signaling mediates early demyelination induced by leprosy bacilli,Nat Med. 2006; 12:961 966.
11. Schlesinger LS, Horwitz MA,Phagocytosis of *Mycobacterium lepra*eby human monocyte-derived macrophagesis mediated by complement receptors CR1 (CD35), CR3(CD11b/CD18), and CR4 (CD11c/CD18) and IFN-*γ* activationinhibits complement receptor function and phagocytosisof this bacterium,J Immuno.1991; 147: 1983–1994.
12. Prabhakaran K, Harris EB, Randhawa B,Regulation by protein kinase of phagocytosis of *Mycobacterium lepra*eby macrophages,J MedMicrobiol.2000; 49: 339–342.
13. Montestruc E, Berdonneau R,2 New cases of leprosy in infants in Martinique, Bulletin de la Soci´et´e de PathologieExotique et de ses Filiales.1954; 47: 781–783.
14. Pinheiro RO, Salles JDS, Sarno EN, Sampaio EP,Mycobacterium leprae-

host-cell interactions and genetic determinants in leprosy: an overview,Future Microbiology. 2011;6: 217–230.
15. Leprosy elimination, World Health Organization, http://www.who.int/lep/en/. August 2010.
16. Global strategy for further reducing the leprosy burden and sustaining leprosy control activities, Operational Guidelines, Geneva, World Health Organization. 2006.
17. World Health Organization. Leprosy (Hansen disease). Report by Secretariat. Executive Board, Geneva. 2010.
18. Leprosy Elimination, Clinical classification, World Health Organization. http://www.wpro.who.int/sites/leprosy/leprosy_wpr/leprosy_classification.htm.2010.
19. Lewallen S, Prevention of blindness in leprosy: an overview of the relevant clinical and programme planning issues, Ann Trop Med Parasitol. 1997; 91:341-348.
20. Getahun H, Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes, Lancet.2007;369:2042-49
21. Haslett PA, Roche P, Butlin CR, Macdonald M, Shrestha N, Manandhar R, Effective treatment of erythema nodosumleprosum with thalidomide is associated with immune stimulation, J Infect Dis. 2005; 192:2045-2053.
22. Graham A, Furlong S, Margoles L, Owusu K, Franco PC, Clinical management of leprosy reactions, Infect Dis ClinPract. 2010;18:235-238.
23. Ooi WW, Moschella SL, Update on leprosy in immigrants in the United States: status in the year 2000, Clin Infect Dis. 2001;32:930-937.
24. Smith CM, Smith WC, Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis, MILEP2 Study Group. Mucosal Immunology of Leprosy. J Infect.2000; 41:137-42.
25. Brakel WHV, Nicholls PG, Das L, Barkataki P,Suneetha SK, Jadhav RS,The INFIR Cohort Study: investigating prediction, detection, and pathogenesis of neuropathy and reactions in leprosy, Methods and baseline results of a cohort of multibacillaryleprosy patients in North India,Lepr Rev. 2005;76:14-34.
26. BrakelVWH, Nicholls PG, Wilder-Smith EP, Das L, Barkataki P, Lockwood DNJ, Early diagnosis of neuropathy in leprosy comparing diagnostic tests in a large prospective study (the INFIR Cohort Study),PLoSNegl Trop Dis 2008;2:212.
27. Lockwood DNJ, Lucas SB, Desikan KV, Ebenezer G, Suneetha S, Nicholls P, The histological diagnosis of leprosy type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis, J ClinPathol. 2008;61:595- 600.
28. Deps PD, Lockwood DNJ, Leprosy occurring as immune reconstitution syndrome, Trans R Soc Trop Med Hyg. 2008;102:966-968.
29. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, et al,Clinical course of erythema nodosumleprosum: an 11-year cohort study in Hyderabad, India, Am J Trop Med Hyg. 2006;74:868-879.
30. Kahawita IP, Lockwood DNJ,Towards understanding the pathology of erythema nodosumleprosum, Trans R Soc Trop Med Hyg. 2008;102:329-33.
31. Setia MS, Steinmaus C, Christine SH, George WR, The role of BCG in prevention of leprosy: a meta-analysis,Thelancet.com.2006; 6.
32. Balagon MF, Cellona RV, Cruz E, Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines, Am J Trop Med Hyg. 2009; 81:895–899.
33. Kaimal S, Thappa DM, Relapse in Leprosy, Indian J DermatolVenereolLeprol. 2009; 75:126–135.
34. Shepard, C. C., R. J. Rees, L. Levy, S. R. Pattyn, J. Baohong, and E. C. Dela Cruz, Susceptibility of strains of Mycobacterium leprae isolated prior to 1977 from patients with previously untreated lepromatous leprosy, Int. J. Lepr. Other Mycobact. Dis. 54:11–15.

35. World health organization expert committee on leprosy, Fifth Report, World health organization, geneva, switzerland.1977.
36. Balagon MF, Cellona RV, Cruz E, Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines, Am J Trop Med Hyg. 2009; 81:895–899.
37. Burgos J, Cruz EDL, Paredes R, Andaya CR, Gelber RH, The activity of several newer antimicrobials against logarithmically multiplying M. leprae in mice, Lepr Rev. 2011; 82:253–258.
38. Dhople AM, Search for newer antileprosy drugs, Indian. J Lepr. 2000;71:7-22.
39. Hamilton-Miller JM, Shan S, Comparative invitro activity of ketolide HMR 3647 and four macrolides against gram-positive cocci of known erythromycin susceptibility status, J AntimicrobChemother. 1998;41:649-53.
40. Essen MRV, Kongsbak M, SchjerlingP, Olgaard K, Odum N, Geisler C, Vitamin D controls T cell antigen receptor signalingand activation of human T cells, Nat Immunol. 2010; 11:344–349.