International Journal of Pharmaceutical Research and Development

**ISSN Print:** 2664-6862
**ISSN Online:** 2664-6870
**Impact Factor:** RJIF 8
IJPRD 2024; 6(1): 39-48
www.pharmaceuticaljournal.net
Received: 10-07-2024
Accepted: 15-08-2024

**Priyanka Tanwar**
Department of Pharmacology, Bhagvan Mahavir Institute of Medical Sciences, Sonipat, Haryana, India

**Mamta Naagar**
Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana, Ambala, Haryana, India

**Manish Kumar Maity**
Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana, Ambala, Haryana, India

**Corresponding Author:**
**Priyanka Tanwar**
Department of Pharmacology, Bhagvan Mahavir Institute of Medical Sciences, Sonipat, Haryana, India

# A review on leprosy: Etiology, epidemiology, pathophysiology, risk factors, differential diagnosis, management strategies and treatment modalities

**Priyanka Tanwar, Mamta Naagar and Manish Kumar Maity**

**DOI:** https://doi.org/10.33545/26646862.2024.v6.i2a.58

**Abstract**
Another name for leprosy is Hansen disease. It is a persistent granulomatous infection that mostly affects the skin and peripheral nerves. It is often brought on by *Mycobacterium leprae* and *Mycobacterium lepromatosis*. This illness has to be identified and treated very away to prevent the high rates of morbidity and death that are linked to it. In addition to reviewing leprosy evaluation and treatment, this exercise emphasizes the importance of the interprofessional team in diagnosing and treating leprosy patients.

**Keywords:** Leprosy, *Mycobacterium leprae*, Peripheral nerves, Granulomatous infection

## Introduction
Leprosy often brought on by *Mycobacterium leprae* and *Mycobacterium lepromatosis*. *M. leprae* and *M. lepromatosis* together up the "Mycobacterium leprae complex" [1]. Despite having distinct DNA sequences that lead to various taxonomic classifications, both mycobacteria are obligatory intracellular creatures with many characteristics that lead to the same clinical illness [2]. In present situation, the medical world is very concerned about leprosy. Contrary to popular assumption, this condition is not very communicable, and treatment for it is easily accessible [3, 4]. There is a chance to significantly reduce the amount of impairment affecting the hands, feet, and eyes with early medical intervention and awareness. Although neuropathy seldom recurs, any damage it causes is permanent and may need lifetime care [5].

## Etiology
Gram-positive, acid-fast bacilli is *Mycobacterium leprae*. It includes both *M. lepromatosis* and *M. leprae*. The former of these two has a generation time of around 12 - 13 days, and it multiplies more slowly than the later. This obligatory intracellular organism has fewer than half of the genes for functional tuberculosis and cannot be cultivated in artificial medium. According to lab testing, *M. leprae* grows at temperatures between 27 – 33 ˚C. This supports the original notion of *M. leprae*'s propensity to propagate more quickly in colder body areas. This covers the skin, the membranes in the upper respiratory tract, and the nerves near the skin's surface [4]. The nine-banded armadillos, which are mostly found in south-central United States and have a core temperature of 34˚C normally, are another animal species in which this strain thrives strongly [6]. In addition to armadillos, *M. leprae* has also been found in chimpanzees, mangabey monkeys, and cynomolgus macaques [7]. The genomes of *M. leprae* and *M. lepromatosis* have been identified, and they demonstrate that both strains' genetic composition includes a significant amount of pseudogenes. Moreover, a number of genes necessary for the function of essential enzymes in metabolic pathways are absent [2, 8, 9]. The overabundance of pseudogenes has facilitated the robust development of mycobacteria under the categorization as an obligatory intracellular organism. Differential nucleotide polymorphisms have been observed in *M. lepromatosis* de novo sequencing. This has made it possible for scientists to formulate the theory that more than 13 million years ago, *M. leprae* and *M. lepromatosis* separated from a common ancestor [1, 2].

**Epidemiology**

The World Health Organization (WHO) declared leprosy to be totally eliminated in 2000. The final definition of infection eradication was the total decrease in prevalence to less than 1 case per 10000 individuals. Between 1985-2011, the number of cases reported decreased from 5.4 million to about 219000. With the exception of Europe, the prevalence rate fell from around 21.1 to 0.37 per 10000 persons by 2011 [10]. The majority of leprosy cases occur in improving nations, while prevalence varies. In 2009, around 1600 nations reported roughly 1000 new cases. The majority of instances were found to be in Bangladesh, Brazil, Nigeria, India, and Indonesia [5]. These leprosy data reveals that not all instances are recorded. When door-to-door initiatives were undertaken in Bangladesh, the number of cases increased by over five times when compared to the results of self-reporting alone. Immigrants were found to be involved in 75% of incidents in the United States. International exposure was a contributing factor in some incidences of leprosy cases among nationals of the United States of America. Exposure by infected armadillos was also demonstrated to be a possibility, if not from another person [11, 12, 13]. Also when looking at gender specificity, leprosy is observed more in men with an approximate 3 to 2 ratio. Multibacillary cases were reported to account for 61% of new patients in 2009; worldwide, this percentage ranged from 33 to 94%.

**Pathophysiology**

Though its exact mode of transmission is unknown, leprosy is thought to be spread by respiration. Lepromatous infection patients who are left untreated typically have a high bacillus count [14, 15]. Once within the body, the main mechanism of diffusion begins in the upper respiratory tract. According to reports, a host infection may also result from a skin break. *M. leprae* causes nerve demyelination and loss of axonal conductance, which manifests numbness. This is occurred by targeting Schwann cells (SCs), which are the target of *M. leprae*'s attraction for peripheral nerve cells [16]. The main method of *M. leprae*'s dissemination as well as the environmental factors that support the microbe is now under investigation. *M. leprae* has demonstrated vitality and resilience following consumption by amoebae [17, 18]. Additionally, it has been seen to remain viable for up to eight months [19]. Additionally, it has been observed that ticks aid in transmission by passing the bacterium to their eggs [20]. With the modern-day technical breakthroughs in molecular identification, more researches may be done to discover reservoirs and vectors to determine viability. It is crucial to remember that many people do not get the illness after their initial exposure. Numerous variables, such as immune system performance and genetic predisposition, influence the disease's growth and progression. While the Th2 immune response is weak and leads to greater bacterial numbers and more severe disease, the Th1 immune response is powerful and is linked to lower bacterial counts and restricted disease.

**Risk factors**

Leprosy has spread due to a number of factors. These are –

1. **Close Contact:** Compared to the general population, the likelihood of contracting leprosy increases significantly when one has direct contact with a patient who has the illness [21].
2. **Armadillo Exposure:** The *M. leprae* strain is indigenous to the nine-banded armadillo in the southern United States. Molecular typing techniques have established the animal-to-human transfer of the bacterium, despite the fact that the exact mode of transmission from armadillos to people is still unknown [11].
3. **Age:** An increased risk of contracting leprosy is associated with older members of society. There is a bimodal link between age and several studies. Risk was elevated from 5 to 15 and remained high beyond 30 [22].
4. **Genetic Influences:** As was already said, immunity is influenced by heredity. Genetic influences are responsible for innate immunity, particularly through the PARK2/PACRG gene [23]. A study including 21,000 contacts and over 1000 individuals recently diagnosed with leprosy demonstrated the significance of genetic relationships. Regardless of the degree of interaction, these relationships supported genetics as a significant risk factor [22].
5. **Immunosuppression:** There's a higher likelihood of contracting this virus after immune system suppression. Leprosy usually develops following solid organ donation, HIV infection, chemotherapy, or medication administration for rheumatologic symptoms [s].

**Histopathology**

Leprosy manifests histopathologically in a variety of ways, depending on how the cellular immune system reacts to the *M.leprae* complex [27].

1. **Tuberculoid leprosy (TT) and borderline tuberculoid (BT):** Characterized by infiltration of dermis and subcutaneous fat with well-defined epithelioid non-caseating granulomas and few or absent acid-fast bacilli (AFB).
2. **Lepromatous leprosy (LL) and borderline leprosy (BL):** Consists of macrophages with a vacuolar cytoplasm, plasma cells, lymphocytes, and numerous acid-fast bacilli (AFB).

**Clinical presentation**

Leprosy manifests itself in a multitude of ways, mostly because of the widespread immunological reaction to the *M. leprae* strain. The whole depth of the clinical characteristics is covered by the Ridley-Jopling categorisation system. From a modest number of tuberculoid organisms and a strong immune response to a weak reaction and an increased quantity of multibacillary cells. In general, the body's cutaneous, biopsy, and neurologic results are used to apply this categorisation. This provides a realistic assessment of the immunological response that will be generated for medical experts. The acid-fast bacilli found in the dermis are likewise connected to the previously reported results. This includes: Tuberculoid (TT), Borderline tuberculoid (BT), Mid-borderline (BB), Borderline lepromatous (BL), Lepromatous (LL), Indeterminate (I) [28, 29]. The condition manifests itself in different degrees of severity. Presentation comprises of well-demarcated lesions with central hypopigmentation and hypoesthesia in instances with a markedly increased cell-mediated immune response and delayed hypersensitivity. This inflammatory granulomatous growth is explicitly mentioned as a polar tuberculoid. It is also associated with unusual acid-fast bacilli in the tissues. People that do not exhibit any resistance to the *M. leprae*

strain are found to have several elevated, poorly defined lesions all over their bodies. This kind of infection is known as polar lepromatous because it causes a significant amount of illness. Notably, these individuals do not exhibit a history of immunosuppression; still they are unable to develop immunity against *M. leprae*. When lesions first appear, they are seen as widespread perineural invaders with perhaps acid-fast bacteria. It is further classified as uncertain in the absence of established establishment criteria. Typically, children with spontaneous healing appear with these situations. It is advised that this categorization be used only in cases when biopsy results reveal leprosy; it is not severe enough to be locked in on a spectrum. Before being labelled as such, indeterminate situations should ideally be verified by a lab test or by eye inspection.

A different categorization profile was created for situations in which there would be little access to lab or clinical help. This approach is based on the number of lesions present. Paucibacillary (PB) leprosy would be diagnosed in cases with five or fewer skin lesions and no visible bacilli on skin smears. When only one lesion is visible, the condition is known as a single lesion PB. Multibacillary (MB) leprosy is defined as six or more lesions that provide positive results on a skin smear test. Additional physical features evident when considering leprosy includes symptoms such as: Reddish skin patches with sensory loss, Paresthesias with associated numbness in extremities, Painless burns in extremities, Lumps or swelling on the earlobes, Enlarged sensitized peripheral nerves. After substantial development, some findings include facial paralysis, weakening in the claw fingers, absence of the eyebrows and eyelashes, or a perforated nasal septum. In general, the degree of nerve immersion, the kind of categorisation, and any active immunological reactions determine how severe the symptoms are.

The following subsections provide categories for skin lesions that are often observed in leprosy patients:

| | |
|---|---|
| Tuberculoid leprosy (TT) | Large, well defined, raised-margin, hypopigmented, or erythematous lesions are the initial signs of this. Scaly plaque presentation was demonstrated. |
| Borderline tuberculoid (BT) | Macules in lesions that have a "target" look are known as BT. More lesions than TT are present in this particular condition, and they often only affect one side of the body. According to the WHO categorization indicated above, these kinds of lesions are referred to as "paucibacillary." |
| Mid-borderline (BB) | Known as "multibacillary," this illness most resembles border-lepromatous or BT leprosy due to the look of "punched out" lesions. Take note that most of the centre regions are anaesthetic. |
| Borderline lepromatous leprosy (BL) | In this instance, lesions are erythematous macules, nodules, or papules that do not exhibit a recognizable pattern of physical appearance on the body. Even if there are normal skin patches present, the lesions are dispersed and difficult to distinguish. It has been demonstrated that the distribution of larger lesions is disproportionate. |
| Lepromatous leprosy (LL) | Significantly advanced instances have nodule growth of the earlobes in addition to loss of body hair [30]. Mucosal invasion can have a stuffy appearance, much like the common cold. If treatment is not promptly sought after, a ruptured septum or collapse may result. With sporadic bacteremia throughout this illness, asymptomatic presentation is also conceivable. In this instance, M. leprae advances with localised lesions in many organs [31]. After a request for a biopsy, there are several circumstances where organisms are found in the liver or bone marrow [32]. It is also possible for the larynx and testicles to become involved [33]. |
| Indeterminate disease | Appears as a macule that is erythematous or hypopigmented and has little to no feeling. This biopsy often does not include Bacilli. Should the lesion appear underdeveloped, it should transform into a different kind within the spectrum of leprosy. |

**Other clinical conditions**

**Neuropathy:** Early on in the leprosy course, nerve association is seen as evidenced by a general loss in feeling in lesions [4]. One of the main objectives is to reduce damage to peripheral nerves and accurate examination of these nerves is essential for accurate assessment. Neuropathy usually starts with loss of sensory experience, but later in the course of the disease, pain can also occur [34, 35]. Depending on the nerves around the skin lesion, people with tuberculoid illness may experience sensory and motor loss. When lepromatous illness is present, the harm is more widespread. The median nerves, peroneal nerve, posterior tibial nerve, facial nerve, and great auricular nerve are among the body's nerve trunks that are affected. Subclinical neuropathy appears to be more prevalent than first thought [36]. Experiments employing sensitive techniques, such as monofilaments have demonstrated that nerve damage starts earlier in lepromatous illness than in tuberculoid disease [37-39]. Heat perception and sensory nerve conduction were among the standard tests. These tests' findings typically started to show abnormalities three months or longer before they could be identified with monofilaments [40]. Segmental demyelination is a recurring element in this disease's ultimate manifestation of nerve damage [4, 36, 41]. Despite being little known, broad approaches to investigate the disease's pathophysiology are challenging. Due to the significant involvement of peripheral nerve trunks, a full biopsy of the tissues affected by this illness is not possible.

**Ophthalmic Injury:** Diminished nerve innervation linked to the muscles in the eyelids and sending a signal to the cornea may result in lagophthalmos, ulcerations and abrasions of the cornea, and dryness. Complete ocular evaluation is necessary for thorough exams.

**Immunologic Reactions:** These kinds of responses are systemic in nature and may manifest either before to the initiation of treatment, during treatment, or even a considerable amount of time after treatment has finished [42]. Leprosy responses fall into two categories: T1R (Type 1 reversal reaction) and T2R or erythema nodosum leprosum (ENL). T1R is involved in patients with borderline illness but T2R is often involved in lepromatous disease. Additional research is necessary to fully understand both of these reactions including the mechanisms of response and the overall conditions necessary for them to occur [4]. Fatigue, malaise, and fever are possible in all response types, along with additional manifestations such as nasopharyngeal symptoms, arthritis and neuritis. Paralysis and deformities may result from immunological responses causing nerve damage. It is crucial to understand that medications do not cause these side effects, and the

prescribed course of therapy should continue. A summary of the responses that were previously mentioned is as follows:

**Type 1 Reaction (T1R)**
Typically comes up in BT, BB or BL cases. Presentation includes:

- Red, swollen areas with existing lesions associated with nerve trunk or face
- Erythema of skin lesions present
- Inflammation due to reactions leading to deformity and paralysis
- Edema
- Ulceration of lesions on the skin
- Weakness or loss of nerve function

The T1R pathway lasts for around two months in the absence of therapy. Subsequent research has demonstrated that this response seems to result from both impeded hypersensitivity to *M. leprae* antigens and the unhindered development of cell immunity [4]. Biopsies may reveal granulomatous appearance, increased multinucleated cell count and oedema [43]. In some situations, it is unclear exactly what broad initial event initiated the trend. It becomes extremely difficult to forecast which people may get this condition as a result [44]. To reduce the likelihood of responses no changes to the regimen should be made.

**Type 2 Reaction (T2R, ENL)**

- Presented in individuals with BL and LL
- The scale has been developed to further support physicians in further understanding the specific case [45].

Type 2 responses often manifest as painful nodules that appear suddenly and can be deep or superficial in the dermis. When pus is discharged excessively pustules may occur. It is demonstrated that the exudate contains acid-fast bacilli and polymorphs. Lesions often last a few days and are mostly found on the surfaces of the face and arms. There is a very rare syndrome known as the Lucio phenomenon that can occur in Type 2 reaction instances and shows up as necrotising vasculopathy in patients with lepromatous leprosy that has gone untreated [46]. Three well-established risk factors for Type 2 diabetes include puberty, pregnancy, and breastfeeding [47]. There is still much to learn about the general processes behind this type 2 response. Though the statistics do not support this view, researchers and doctors believe that this immune response is related to complexes [4]. Although elevated levels of TNF-alpha in conjunction with other cytokines have been seen, their overall process-influencing effect is yet unknown. It has been shown that T and B cells undergo modification during ENL, and neutrophils are also present in the lesions [48-50].

**Assessment Procedures**
Histopathological investigation utilizing skin samples and PCR was the main focus of laboratory method development. The following findings were typical when assessing for leprosy by laboratory testing: raised leukocyte counts, reduced haemoglobin levels, poor haematocrit, abnormal liver function tests and elevated serum C-reactive protein [51].

**Skin Biopsy:** A thorough biopsy including subcutaneous tissues is advised for the lesion's most dynamic and active margin based on the severity of the lesions and the degree of nerve infiltration. The previously noted extreme change in the spectrum is displayed using haematoxylin and eosin sectioning. Polymorphonuclear leukocytes are a defining feature of type 2 responses, whereas fibrin thrombi are clearly seen in lesions referred to as Lucio's phenomenon. Studies to better establish histologic criteria for type 1 responses are presently being conducted. Making ensuring that cutaneous diseases, such as *M. tuberculosis* and non-tuberculin mycobacteria, are excluded from potentially interfering with the evaluation of the mycobacterial cultures is a crucial step in the evaluation process.

**Polymerase Chain Reaction:** The laboratory method DNA from *M. leprae* and *M. lepromatosis* may be easily found in tissue using PCR [52]. As a detector as opposed to an identifier PCR is more useful. Biopsy PCRs demonstrated a sensitivity of over 90% and a specificity of 100% in the present trials. Results indicated 34 percent sensitivity and 80 percent specificity in instances with tuberculoid illness. Proteins and peptides that are still present in the sample are eliminated during the creation of skin tests leaving just *M. leprae* [53]. Another technique called the "lepromin test" involves injecting autoclaved *M. leprae* that has been calibrated and then evaluated on the skin after three to four weeks. A positive result from this approach implies exposure to the strain and suggests that a granuloma may develop after exposure but it also indicates exposure to the leprosy in question [54]. It was observed in a highly endemic location that only 15% to 50% of diagnosed leprosy patients showed a favourable response compared to 70% of controls [55].

**Serologic Test:** The specific *M. leprae* phenolic glycolipid-1 (PGL-1) is mentioned in serology investigations, however it is not frequently used in US clinical practice procedures because it lacks clinical and histological support [56-58]. When *M. leprae* phenolic glycolipid-1 (PGL-1) is tested, people with lepromatous illness typically show an increased polyclonal immune response and several false-positive responses. Since PGL1 antibodies are not usually induced by tuberculoid illness, this method of testing is invalid for this particular group of individuals [59-61]. In conclusion PGL1 has not been shown to be semi-predictive or even confirmatory of the emergence of infection. Studies on serology are still improving and deepening our understanding of current practices [62, 63].

**Management strategies and treatment modalities**
Multiple drug therapy (MDT) is typically used in the general treatment of leprosy in order to prevent germ resistance. The patient is rapidly brought to a non-infectious state by the MDT therapy, which is effective against *M. leprae*. Additionally using MDT lowers the likelihood of medication resistance [64]. Dapsone, rifampin, and clofazimine are among the medications utilised; the latter is recommended for lepromatous illness. These medications work best when used together [65]. Conventional leprosy treatment is effective against both *Mycobacterium leproe* and *Mycobacterium lepromatosis* [66, 67]. Historically, the initial antimicrobial agent used for the treatment of leprosy was promine, a sulfone. The effectiveness of this sulphate was further shown with dapsone, a similar substance [68, 69]. But after a while of monotherapy the strain showed signs of

resistance to this medication [70]. The World Health Organisation released a guideline in 1982 for the treatment of lepromatous leprosy, which called for the use of dapsone and rifampin in conjunction with clofazimine [71]. In addition to mice studies, clinical evidence has been provided for the drugs' efficacy [72-74]. As of right now, no controlled studies have been conducted to compare the various medication combinations. It is hard to design studies with an appropriate endpoint and a long enough observation period to identify recurrence.

Treatment is as follows:

- **Tuberculoid disease:** dapsone (100 mg daily) with rifampicin (600 mg daily) for 12 months
- **Lepromatous disease:** dapsone, rifampicin, and clofazimine (50 mg daily) for 24 months

The treatment approach presented by the United States National Hansen's Disease Program (NHDP) is usually the general consensus [71]. There has been advocacy for daily rather than monthly doses of rifampin coupled with longer treatment times [75]. The recommended treatment timeline by WHO in 1982 was 0.5 to 1 year for tuberculoid disease (TT/BT) and 2 years for lepromatous disease (BB/BL/LL) [71]. In 2018 WHO guidelines now advise for uniform MDT with the recommendations for treatment from 1998 still maintained. This entails administering three drugs: rifampin, dapsone and clofazimine to individuals despite the classified type. The daily addition of clofazimine for the paucibacillary illness marks a departure from previous regimens. The number of multibacillary instances has not changed. Reducing the likelihood of undertreating patients with multibacillary illness who are mistakenly labelled as paucibacillary by using the standardised MDT therapy. A few other medications that could be employed include clarithromycin, levofloxacin, ofloxacin, moxifloxacin, and minocycline. To prove the general efficacy of these medications more research is required [76]. After 18 months, a trial combining 600 mg of rifampin, 100 mg of minocycline, and 400 mg of ofloxacin showed less progress than a typical paucibacillary therapy regimen [77]. According to other researches, treating lepromatous (MB) illness with a one-month trial of rifampin and ofloxacin was insufficient [78]. The overall erythema and hardness of the lesions should go away after a few months of medication. On the other hand, lesions affecting cutaneous characteristics could not totally resolve for a few years. Depending on the overall quantity of lesions and the intensity of the infection each case is unique. Bacilli killed by the treatment are removed from tissues at a decreased rate, lasting for a couple of years [79]. Because *M. leprae* and *M. lepromatosis* cannot be cultured, there is no overall therapeutic objective for the therapy. Furthermore, the presence of bacilli in tissues alone cannot conclusively determine the efficacy of a therapy. The elimination of dead bacilli from body tissues and therapy has not been shown to be correlated. Research has indicated that *M. leprae* is more quickly destroyed when it comes into touch with rifampin and other medications [80]. By using NHDP and WHO methods, doctors have recently observed good outcomes with MDT, with a low rate of relapses. These outcomes represent patients that received therapy for one to two years [5]. Therefore there is a high probability that bacilli eradication and total lesion resolution can be achieved by following the MDT protocol.

Inflammatory reactions known as immune reactions typically occur prior to, throughout or even months or years after the completition of regimen [81]. Other presentations such as arthritis, neuritis or nasopharyngeal symptoms might also cause fatigue and fever. Inflammation increases the risk of nerve damage, which can result in deformity and paralysis.

- **Type 1 Reactions:** With assistive care, mild instances without symptoms like ulceration or neuritis might be handled cautiously. To reduce irreparable nerve damage in severe neuritis cases, prompt therapeutic intervention with corticosteroids may be necessary [82]. It is advised to take 40–60 mg of prednisone each day, gradually lowering the dosage when the condition is under control. In cases when patients experience severe responses, prolonged corticosteroid therapy may be necessary due to significant nerve issues. Research has demonstrated that higher dosages and longer durations of corticosteroids are more beneficial in reducing pain and inflammation than are lower and shorter dosages [83]. Corticosteroid prophylaxis does not appear to have a significant impact in lowering type 1 responses [84]. Methotrexate can take the place of a steroid treatment in diabetic individuals [85]. Cyclosporine is a helpful secondary therapeutic option for type 1 responses in people who do not respond well to corticosteroid treatment [4]. In certain instances, this medication has been demonstrated to aid with nerve damage and lesions; nevertheless, toxicity was also observed [86, 87].
- **Type 2 reaction (T2R):** Clinical treatment that is thoroughly thought out can be used to treat mild responses. Corticosteroids are given right away to treat severe type 2 reactions in order to protect nerve tissue. 40–60 mg of prednisone per day is administered until the condition is under control. Once control is obtained it is advised to progressively reduce the dose over a minimum of two weeks. If longer treatment is required varying the dosage according to a different schedule each day may help reduce the overall negative effects of the steroids [88]. While clofazimine has no impact on acute type 2 responses, it is useful in chronic instances. Dosages should be increased to around 300 mg per day for one month and then gradually lowered to 100 mg per day over the course of a year. As clofazimine was used less after MDT became well-known, it could play a part in protecting against certain responses. In the US, a prescription for clofazimine necessitates an FDA investigational medication request. Although thalidomide is thought to be a very effective treatment for type 2 responses, it may have negative effects on women who are able to carry children [89]. The main justification for thalidomide's continued use in medicine is its effectiveness. Within 48 hours, the body's response is under control thanks to the first dose of 300–400 mg per day. Following the start of therapy, the dosage needs to be reduced every few months to a maintenance concentration of about 100 mg per day. Thalidomide treatment can continue for several years in an effort to manage erythema nodosum leprosum. As neuropathy progresses, therapy should be stopped right away. Although cytokines are not frequently used to treat leprosy, considerable research has been done on their potential benefits. Numerous type 2 response patients have been seen to benefit with TNF-alpha

inhibition [90, 91]. Unbeknownst to the doctors, giving these medications to patients with severe arthritis may put them at risk of developing leprosy [26]. Intralesional injection of interleukin-2 or interferon has showed promise in the treatment of lepromatous leprosy. However, it has been observed that the administration of this medication has unintentionally increased the percentage of type 2 reaction development [92-96].

**Differential Diagnosis**

The patient's inability to detect any kind of sensory stimuli in the lesion, from gentle touch to pinprick is a confirmatory sign of leprosy. Typically, a skin biopsy is used to establish the diagnosis. The following are included in differential:

- **Granuloma annulare:** The appearance is a scale-less, erythematous plaque with marginal papules that is asymptomatic. Usually, the border has a clearing in the middle and resembles a rope. In general the hands, feet, ankles, and wrists are the locations of manifestation.
- **Fungal infection:** A scaling, circular, erythematous patch with a radial distribution and clearing is the initial sign of a fungal infection. Along with being elevated, the border is erythematous. Preparing potassium hydroxide is the process for confirming the diagnosis.
- **Annular psoriasis:** Though it happens infrequently, this annular lesion is not particularly prevalent in people with psoriasis. The identification of psoriasis signs, such as typical plaques and nail disease, which are occurring more frequently, is linked to the diagnosis of this condition. A biopsy is required in order to be certain.
- **Systemic lupus erythematosus:** Lupus can present as either localised (Butterfly rash) or widespread cutaneous lesions. When skin is exposed to sunlight from the outside, further erythematous macular eruption also happens.
- **Keloid:** Dermal lesions near the wound site that have an elevated look are called keloids. Progression to regions adjacent to the main site may result in an extension of the wound beyond its original confines.
- **Mycosis fungoides:** The cutaneous appearance is non-uniform and includes baldness, erythroderma, tumours, and patches. A skin biopsy is used for diagnostic confirmation.
- **Neurofibromatosis:** Cutaneous appearance includes freckles in the inguinal region, axilla and cafe-au-lait macules. Neurofibromas are also present in this instance. The main criteria used to establish this case are clinical features.
- **Cutaneous leishmaniasis:** These types of lesions often affect exposed skin regions. Pink papules that expand into nodules are the initial stage of local instances. Nodule development is followed by localised hardness and the beginning of painless ulceration.

In type 1 reactions, the diagnosis is usually completed just using clinical evaluation. Typical lab exams are not readily available for aid in diagnosis. High serum levels of chemokine CXCL10 have been shown to be related to type 1 reactions. CXCL10 should not be considered as an indicator for T1R. CXCL10 is not shown to be present in high concentrations in advance of the reaction; hence there is low confidence in its predictive ability [97, 98].

**Prognosis**

The leprosy patient's prognosis is contingent upon several circumstances, such as the disease stage at diagnosis, prompt treatment beginning, treatment accessibility, and therapy compliance. Leprosy is usually considered treatable if multidrug treatment (MDT) is initiated soon after the disease first manifests. Neurological impairment and severe deformities can be avoided with MDT therapy. It is possible to limit the degree of neurologic impairment by appropriately following the prescribed treatment plan. However, some cases have demonstrated that there is only a partial or complete recovery from any muscular weakness or sensory loss that existed prior to the initiation of treatment. When MDT is used, there is very little chance of relapse; the illness returning after treatment is finished and deaths are also rare.

**Complications**

Leprosy patients still have the potential for nerve abscesses to develop. This kind of problem, which is typically observed on the ulnar nerve, needs to be surgically treated very once in order to avoid permanent consequences. In addition to cranial nerve palsies, nerve-related issues can also affect the eyes resulting in corneal insensitivity and lagophthalmos. This may result in corneal ulcerations and opacities, as well as damage and infection. There is a correlation between the number of positive leprosy cases and blindness in third-world nations. Another leprosy-related consequence is neuropathy in the extremities, which results in loss of distal digits by impairing sensitivity to pain, heat, and delicate touch. In cases involving patients with leprosy, the loss of distal sensitivity is possible, although this process is not fully understood and could be some ill-understood osteolytic process. In inflamed immunological reactions, chances of morbidity are high. Erythema nodosum leprosum (ENL) is usually presented with painful erythematous papules that resolve within a week. This type of papule occurs in nearly 50% of individuals closer to the LL type of leprosy. Apart from the damage caused to skin and peripheral nerves mostly it also involves reticuloendothelial, endocrine and hemopoietic systems along with muscles, bones and eyes [99]. Previous researches indicate that medication resistance in *M. leprae* is not readily apparent. A research evaluating antimicrobial resistance showed that the approximate rates of drug endurance were 1.3% for ofloxacin, 5.3% for dapsone, and 3.8% for rifampin among more than 1900 patients between 2009 and 2015. These results suggest that the number of isolates exhibiting resistance is still increasing [100].

**Patient counselling**

In terms of controlling measures, contact management which encompasses both contact control and the care of patients who are actively ill; it is crucial for leprosy. For a minimum of five years household contacts of affected individuals should be evaluated annually and urged to seek medical attention right once in the event that any questionable symptoms such as skin or neurological abnormalities appear. Leprosy is somewhat preventable with the BCG vaccine; 50% protection is achieved with a single dosage, while more protection is obtained with a double dose [101, 102]. In regions where leprosy is exceedingly common infants are immunised against disease with the BCG vaccine [103]. A single dosage of rifampin is

recommended for adults and children over the age of two in WHO 2108 recommendations for prophylaxis in endemic regions. Research is being done to demonstrate the advantages of this approach [104]. In addition to attempting to lessen the cultural stigma associated with leprosy patients should be informed about the diagnosis, course of treatment, prognosis, and problems associated with the illness.

## Conclusion

Like any other illness, leprosy calls for an interdisciplinary approach and collaboration between primary care doctors, infectious disease experts, nurses and chemists. Encouraging patient care and improving healthcare results greatly depend on appropriate counselling of the illness process, treatment plan, compliance, significance of routine follow-up and emotional and mental health support from all parties engaged in the patient's care including family and friends.

## References


1. Singh P, Benjak A, Schuenemann VJ, Herbig A, Avanzi C, Busso P, *et al*. Insight into the evolution and origin of leprosy bacilli from the genome sequence of Mycobacterium lepromatosis. Proc Natl Acad Sci U S A. 2015 Apr 07;112(14):4459-64.
2. Han XY, Sizer KC, Thompson EJ, Kabanja J, Li J, Hu P, *et al*. Comparative sequence analysis of Mycobacterium leprae and the new leprosy-causing Mycobacterium lepromatosis. J Bacteriol. 2009 Oct;191(19):6067-74.
3. Moschella SL. An update on the diagnosis and treatment of leprosy. J Am Acad Dermatol. 2004 Sep;51(3):417-26.
4. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev. 2006 Apr;19(2):338-81.
5. Global leprosy situation, 2010. Wkly Epidemiol Rec. 2010 Aug 27;85(35):337-48.
6. Truman R. Leprosy in wild armadillos. Lepr Rev. 2005 Sep;76(3):198-208.
7. Valverde CR, Canfield D, Tarara R, Esteves MI, Gormus BJ. Spontaneous leprosy in a wild-caught cynomolgus macaque. Int J Lepr Other Mycobact Dis. 1998 Jun;66(2):140-8.
8. Cole ST, Eiglmeier K, Parkhill J, James KD, Thomson NR, Wheeler PR, *et al*. Massive gene decay in the leprosy bacillus. Nature. 2001;409(6823):1007-11.
9. Eiglmeier K, Parkhill J, Honoré N, Garnier T, Tekaia F, Telenti A, *et al*. The decaying genome of Mycobacterium leprae. Lepr Rev. 2001;72(4):387-98.
10. Global leprosy situation, 2012. Wkly Epidemiol Rec. 2012 Aug 24;87(34):317-28.
11. Truman RW, Singh P, Sharma R, Busso P, Rougemont J, Paniz-Mondolfi A, *et al*. Probable zoonotic leprosy in the southern United States. N Engl J Med. 2011 Apr 28;364(17):1626-33.
12. Domozych R, Kim E, Hart S, Greenwald J. Increasing incidence of leprosy and transmission from armadillos in Central Florida: A case series. JAAD Case Rep. 2016 May;2(3):189-92.
13. Sharma R, Singh P, Loughry WJ, Lockhart JM, Inman WB, Duthie MS, *et al*. Zoonotic Leprosy in the Southeastern United States. Emerg Infect Dis. 2015 Dec;21(12):2127-34.
14. Abraham S, Mozhi NM, Joseph GA, Kurian N, Rao PS, Job CK. Epidemiological significance of first skin lesion in leprosy. Int J Lepr Other Mycobact Dis. 1998 Jun;66(2):131-9.
15. Araujo S, Freitas LO, Goulart LR, Goulart IM. Molecular Evidence for the Aerial Route of Infection of Mycobacterium leprae and the Role of Asymptomatic Carriers in the Persistence of Leprosy. Clin Infect Dis. 2016 Dec 01;63(11):1412-1420.
16. Britton WJ, Lockwood DN. Leprosy. Lancet. 2004 Apr 10;363(9416):1209-19.
17. Lahiri R, Krahenbuhl JL. The role of free-living pathogenic amoeba in the transmission of leprosy: a proof of principle. Lepr Rev. 2008 Dec;79(4):401-9.
18. Paling S, Wahyuni R, Ni'matuzahroh, Winarni D, Iswahyudi, Astari L, *et al*. *Acanthamoeba* SP.S-11 phagocytotic activity ON *mycobacterium leprae* in different nutrient conditions. Afr J Infect Dis. 2018;12(1 Suppl):44-48.
19. Wheat WH, Casali AL, Thomas V, Spencer JS, Lahiri R, Williams DL, *et al*. Long-term survival and virulence of Mycobacterium leprae in amoebal cysts. PLoS Negl Trop Dis. 2014 Dec;8(12):e3405.
20. Moss C, Burn J. Genetic counselling in hypomelanosis of Ito: case report and review. Clin Genet. 1988 Aug;34(2):109-15.
21. Van Beers SM, Hatta M, Klatser PR. Patient contact is the major determinant in incident leprosy: implications for future control. Int J Lepr Other Mycobact Dis. 1999 Jun;67(2):119-28.
22. Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. J Infect Dis. 2006 Feb 01;193(3):346-53.
23. Mira MT, Alcaïs A, Nguyen VT, Moraes MO, Di Flumeri C, Vu HT, *et al*. Susceptibility to leprosy is associated with PARK2 and PACRG. Nature. 2004 Feb 12;427(6975):636-40.
24. Trindade MA, Palermo ML, Pagliari C, Valente N, Naafs B, Massarollo PC, *et al*. Leprosy in transplant recipients: report of a case after liver transplantation and review of the literature. Transpl Infect Dis. 2011 Feb;13(1):63-9.
25. Martiniuk F, Rao SD, Rea TH, Glickman MS, Giovinazzo J, Rom WN, *et al*. Leprosy as immune reconstitution inflammatory syndrome in HIV-positive persons. Emerg Infect Dis. 2007 Sep;13(9):1438-40.
26. Scollard DM, Joyce MP, Gillis TP. Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. Clin Infect Dis. 2006 Jul 15;43(2):e19-22.
27. Massone C, Belachew WA, Schettini A. Histopathology of the lepromatous skin biopsy. Clin Dermatol. 2015 Jan-Feb;33(1):38-45.
28. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis. 1966 Jul-Sep;34(3):255-73.
29. Pardillo FE, Fajardo TT, Abalos RM, Scollard D, Gelber RH. Methods for the classification of leprosy for treatment purposes. Clin Infect Dis. 2007 Apr 15;44(8):1096-9.

30. Elinav H, Palladas L, Applbaum YH, Gilead L, Moses AE, Cohen-Poradosu R. Plantar ulcers and eyebrow-hair paucity. Clin Infect Dis. 2006;42(5):684-5, 722-4.
31. Lane JE, Balagon MV, Dela Cruz EC, Abalos RM, Tan EV, Cellona RV, *et al*. Mycobacterium leprae in untreated lepromatous leprosy: more than skin deep. Clin Exp Dermatol. 2006 May;31(3):469-70.
32. Kumar B, Rai R, Kaur I. Systemic involvement in leprosy and its significance. Indian J Lepr. 2000 Jan-Mar;72(1):123-42.
33. Fleury RN, Duerksen F. Emergency in leprosy: involvement of the larynx. Lepr Rev. 2007 Jun;78(2):148-50.
34. Saunderson P, Bizuneh E, Leekassa R. Neuropathic pain in people treated for multibacillary leprosy more than ten years previously. Lepr Rev. 2008 Sep;79(3):270-6.
35. Lasry-Levy E, Hietaharju A, Pai V, Ganapati R, Rice AS, Haanpaa M, *et al*. Neuropathic pain and psychological morbidity in patients with treated leprosy: a cross-sectional prevalence study in Mumbai. PLoS Negl Trop Dis. 2011 Mar 08;5(3):e981.
36. Wilder-Smith EP, Van Brakel WH. Nerve damage in leprosy and its management. Nat Clin Pract Neurol. 2008 Dec;4(12):656-63.
37. Meima A, Saunderson PR, Gebre S, Desta K, Habbema JD. Dynamics of impairment during and after treatment: the AMFES cohort. Lepr Rev. 2001 Jun;72(2):158-70.
38. Richardus JH, Nicholls PG, Croft RP, Withington SG, Smith WC. Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. Int J Epidemiol. 2004 Apr;33(2):337-43.
39. Saunderson P, Gebre S, Desta K, Byass P, Lockwood DN. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. Lepr Rev. 2000;71(3):285-308.
40. Van Brakel WH, Nicholls PG, Wilder-Smith EP, Das L, Barkataki P, Lockwood DN. INFIR Study Group. Early diagnosis of neuropathy in leprosy--comparing diagnostic tests in a large prospective study (the INFIR cohort study). PLoS Negl Trop Dis. 2008 Apr 02;2(4):e212.
41. Scollard DM. The biology of nerve injury in leprosy. Lepr Rev. 2008 Sep;79(3):242-53.
42. Scollard DM. Time and change: new dimensions in the immunopathologic spectrum of leprosy. Ann Soc Belg Med Trop. 1993;73(1):5-11.
43. Lockwood DN, 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 Clin Pathol. 2008 May;61(5):595-600.
44. Ranque B, Nguyen VT, Vu HT, Nguyen TH, Nguyen NB, Pham XK, *et al*. Age is an important risk factor for onset and sequelae of reversal reactions in Vietnamese patients with leprosy. Clin Infect Dis. 2007;44(1):33-40.
45. Walker SL, Sales AM, Butlin CR, Shah M, Maghanoy A, Lambert SM, *et al*., Erythema Nodosum Leprosum International STudy Group. A leprosy clinical severity scale for erythema nodosum leprosum: An international, multicentre validation study of the ENLIST ENL Severity Scale. PLoS Negl Trop Dis. 2017 Jul;11(7):e0005716.
46. Rea TH, Jerskey RS. Clinical and histologic variations among thirty patients with Lucio's phenomenon and pure and primitive diffuse lepromatosis (Latapi's lepromatosis). Int J Lepr Other Mycobact Dis. 2005 Sep;73(3):169-88.
47. White C, Franco-Paredes C. Leprosy in the 21st century. Clin Microbiol Rev. 2015 Jan;28(1):80-94.
48. Negera E, Bobosha K, Walker SL, Endale B, Howe R, Aseffa A, *et al*. New Insight into the Pathogenesis of Erythema Nodosum Leprosum: The Role of Activated Memory T-Cells. Front Immunol. 2017;8:1149.
49. Negera E, Walker SL, Bekele Y, Dockrell HM, Lockwood DN. Increased activated memory B-cells in the peripheral blood of patients with erythema nodosum leprosum reactions. PLoS Negl Trop Dis. 2017 Dec;11(12):e0006121.
50. Polycarpou A, Walker SL, Lockwood DN. A Systematic Review of Immunological Studies of Erythema Nodosum Leprosum. Front Immunol. 2017;8:233.
51. Silva EA, Iyer A, Ura S, Lauris JR, Naafs B, Das PK, *et al*. Utility of measuring serum levels of anti-PGL-I antibody, neopterin and C-reactive protein in monitoring leprosy patients during multi-drug treatment and reactions. Trop Med Int Health. 2007 Dec;12(12):1450-8.
52. Gillis T, Vissa V, Matsuoka M, Young S, Richardus JH, Truman R, *et al*., Ideal Consortium Partners. Characterisation of short tandem repeats for genotyping Mycobacterium leprae. Lepr Rev. 2009 Sep;80(3):250-60.
53. Brennan PJ. Skin test development in leprosy: progress with first-generation skin test antigens, and an approach to the second generation. Lepr Rev. 2000 Dec;71 Suppl:S50-4.
54. Mitra DK, Joshi B, Dinda AK, Rai AK, Girdhar BK, Katoch K, *et al*. Induction of lepromin reactivity in cured lepromatous leprosy patients: impaired chemokine response dissociates protective immunity from delayed type hypersensitivity. Microbes Infect. 2009 Dec;11(14-15):1122-30.
55. Kaplan G, Laal S, Sheftel G, Nusrat A, Nath I, Mathur NK, *et al*. The nature and kinetics of a delayed immune response to purified protein derivative of tuberculin in the skin of lepromatous leprosy patients. J Exp Med. 1988 Nov 01;168(5):1811-24.
56. Butlin CR, Soares D, Neupane KD, Failbus SS, Roche PW. IgM anti-phenolic glycolipid-I antibody measurements from skin-smear sites: correlation with venous antibody levels and the bacterial index. Int J Lepr Other Mycobact Dis. 1997 Dec;65(4):465-8.
57. Buhrer SS, Smits HL, Gussenhoven GC, van Ingen CW, Klatser PR. A simple dipstick assay for the detection of antibodies to phenolic glycolipid-I of Mycobacterium leprae. Am J Trop Med Hyg. 1998 Feb;58(2):133-6.
58. Oskam L, Slim E, Bührer-Sékula S. Serology: Recent developments, strengths, limitations and prospects: A state of the art overview. Lepr Rev. 2003 Sep;74(3):196-205.
59. Douglas JT, Celona RV, Abalos RM, Madarang MG, Fajardo T. Serological reactivity and early detection of

leprosy among contacts of lepromatous patients in Cebu, the Philippines. Int J Lepr Other Mycobact Dis. 1987 Dec;55(4):718-21.
60. Ulrich M, Smith PG, Sampson C, Zuniga M, Centeno M, Garcia V, *et al*. IgM antibodies to native phenolic glycolipid-I in contacts of leprosy patients in Venezuela: Epidemiological observations and a prospective study of the risk of leprosy. Int. J Lepr Other Mycobact Dis. 1991 Sep;59(3):405-15.
61. Chanteau S, Glaziou P, Plichart C, Luquiaud P, Plichart R, Faucher JF, *et al*. Low predictive value of PGL-I serology for the early diagnosis of leprosy in family contacts: results of a 10-year prospective field study in French Polynesia. Int. J Lepr Other Mycobact Dis. 1993 Dec;61(4):533-41.
62. Aseffa A, Brennan P, Dockrell H, Gillis T, Hussain R, Oskam L, *et al*., Ideal Consortium. Report on the first meeting of the IDEAL (Initiative for Diagnostic and Epidemiological Assays for Leprosy) consortium held at Armauer Hansen Research Institute, ALERT, Addis Ababa, Ethiopia on 24-27 October 2004. Lepr Rev. 2005 Jun;76(2):147-59.
63. Dean DA, Davidson AL, Nikaido H. The role of ATP as the energy source for maltose transport in Escherichia coli. Res Microbiol. 1990;141(3):348-52.
64. Ji B. Why multidrug therapy for multibacillary leprosy can be shortened to 12 months. Lepr Rev. 1998 Jun;69(2):106-9.
65. Freerksen E, Rosenfeld M, Depasquale G, Bonnici E, Gatt P. The Malta Project--a country freed itself of leprosy. A 27-year progress study (1972-1999) of the first successful eradication of leprosy. Chemotherapy. 2001 Sep-Oct;47(5):309-31.
66. Sotiriou MC, Stryjewska BM, Hill C. Two Cases of Leprosy in Siblings Caused by Mycobacterium lepromatosis and Review of the Literature. Am J Trop Med Hyg. 2016 Sep 07;95(3):522-7.
67. Scollard DM. Infection with Mycobacterium lepromatosis. Am J Trop Med Hyg. 2016 Sep 07;95(3):500-501.
68. Faget GH, Pogge RC, Johansen FA. Promizole treatment of leprosy. Public Health Rep (1896). 1946 Jun 28;61:957-60.
69. LOWE J. Treatment of leprosy with diamino-diphenyl sulphone by mouth. Lancet. 1950 Jan 28;1(6596):145-50.
70. Pettit JH, Rees RJ. Sulphone resistance in leprosy. an experimental and clinical study. Lancet. 1964 Sep 26;2(7361):673-4.
71. Chemotherapy of leprosy for control programmes. World Health Organ Tech Rep Ser. 1982;675:1-33.
72. Levy L, Ng H, Evans MJ, Krahenbuhl JL. Susceptibility of thymectomized and irradiated mice to challenge with several organisms and the effect of dapsone on infection with Mycobacterium leprae. Infect Immun. 1975 May;11(5):1122-32.
73. Holmes IB, Banerjee DK, Hilson GR. Effect of rifampin, clofazimine, and B1912 on the viability of Mycobacterium leprae in established mouse footpad infection. Proc Soc Exp Biol Med. 1976 Apr;151(4):637-41.
74. Franzblau SG. Drug susceptibility testing of Mycobacterium leprae in the BACTEC 460 system. Antimicrob Agents Chemother. 1989 Dec;33(12):2115-7.
75. Dacso MM, Jacobson RR, Scollard DM, Stryjewska BM, Prestigiacomo JF. Evaluation of multi-drug therapy for leprosy in the United States using daily rifampin. South Med J. 2011 Oct;104(10):689-94.
76. Lockwood DN, Kumar B. Treatment of leprosy. BMJ. 2004 Jun 19;328(7454):1447-8.
77. Landaas S. Inhibition of branched-chain amino acid degradation by ketone bodies. Scand J Clin Lab Invest. 1977 Sep;37(5):411-8.
78. Ji B, Jamet P, Sow S, Perani EG, Traore I, Grosset JH. High relapse rate among lepromatous leprosy patients treated with rifampin plus ofloxacin daily for 4 weeks. Antimicrob Agents Chemother. 1997 Sep;41(9):1953-6.
79. Katoch K, Natarajan M, Bagga A, Katoch VM. Clinical and bacteriological progress of highly bacillated BL-LL patients discontinuing treatment after different periods of MDT. Int J Lepr Other Mycobact Dis. 1991 Jun;59(2):248-54.
80. Franzblau SG. *In vitro* activities of aminoglycosides, lincosamides, and rifamycins against Mycobacterium leprae. Antimicrob Agents Chemother. 1991 Jun;35(6):1232-4.
81. Kamath S, Vaccaro SA, Rea TH, Ochoa MT. Recognizing and managing the immunologic reactions in leprosy. J Am Acad Dermatol. 2014 Oct;71(4):795-803.
82. Walker SL, Lockwood DN. Leprosy type 1 (Reversal) reactions and their management. Lepr Rev. 2008 Dec;79(4):372-86.
83. Rao PS, Sugamaran DS, Richard J, Smith WC. Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. Lepr Rev. 2006 Mar;77(1):25-33.
84. Smith WC, Anderson AM, Withington SG, Van Brakel WH, Croft RP, Nicholls PG, *et al*. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). BMJ. 2004 Jun 19;328(7454):1459.
85. Biosca G, Casallo S, López-Vélez R. Methotrexate treatment for type 1 (reversal) leprosy reactions. Clin Infect Dis. 2007 Jul 01;45(1):e7-9.
86. Marlowe SN, Leekassa R, Bizuneh E, Knuutilla J, Ale P, Bhattarai B, *et al*. Response to ciclosporin treatment in Ethiopian and Nepali patients with severe leprosy Type 1 reactions. Trans R Soc Trop Med Hyg. 2007 Oct;101(10):1004-12.
87. Sena CB, Salgado CG, Tavares CM, Da Cruz CA, Xavier MB, Do Nascimento JL. Cyclosporine A treatment of leprosy patients with chronic neuritis is associated with pain control and reduction in antibodies against nerve growth factor. Lepr Rev. 2006 Jun;77(2):121-9.
88. Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez J, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. Lepr Rev. 2009 Dec;80(4):355-72.
89. Sheskin J. Thalidomide in the treatment of lepra reactions. Clin Pharmacol Ther. 1965 May-Jun;6:303-6.
90. Ramien ML, Wong A, Keystone JS. Severe refractory erythema nodosum leprosum successfully treated with

the tumor necrosis factor inhibitor etanercept. Clin Infect Dis. 2011 Mar 01;52(5):e133-5.
91. Faber WR, Jensema AJ, Goldschmidt WF. Treatment of recurrent erythema nodosum leprosum with infliximab. N Engl J Med. 2006 Aug 17;355(7):739.
92. Nathan C, Squires K, Griffo W, Levis W, Varghese M, Job CK, *et al*. Widespread intradermal accumulation of mononuclear leukocytes in lepromatous leprosy patients treated systemically with recombinant interferon gamma. J Exp Med. 1990 Nov 01;172(5):1509-12.
93. Kaplan G. Recent advances in cytokine therapy in leprosy. J Infect Dis. 1993 Mar;167 Suppl 1:S18-22.
94. Kaplan G, Britton WJ, Hancock GE, Theuvenet WJ, Smith KA, Job CK, *et al*. The systemic influence of recombinant interleukin 2 on the manifestations of lepromatous leprosy. J Exp Med. 1991 Apr 01;173(4):993-1006.
95. Kaplan G, Mathur NK, Job CK, Nath I, Cohn ZA. Effect of multiple interferon gamma injections on the disposal of Mycobacterium leprae. Proc Natl Acad Sci U S A. 1989 Oct;86(20):8073-7.
96. Sampaio EP, Moreira AL, Sarno EN, Malta AM, Kaplan G. Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients. J Exp Med. 1992 Jun 01;175(6):1729-37.
97. Stefani MM, Guerra JG, Sousa AL, Costa MB, Oliveira ML, Martelli CT, *et al*. Potential plasma markers of Type 1 and Type 2 leprosy reactions: a preliminary report. BMC Infect Dis. 2009 May 27;9:75.
98. Scollard DM, Chaduvula MV, Martinez A, Fowlkes N, Nath I, Stryjewska BM, *et al*. Increased CXC ligand 10 levels and gene expression in type 1 leprosy reactions. Clin Vaccine Immunol. 2011 Jun;18(6):947-53.
99. Karat AB. Complications of leprosy. Lepr India. 1978 Jul;50(3):405-13.
100. Cambau E, Saunderson P, Matsuoka M, Cole ST, Kai M, Suffys P, *et al*., WHO surveillance network of antimicrobial resistance in leprosy. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009-15. Clin Microbiol Infect. 2018 Dec;24(12):1305-1310.
101. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. Lancet. 1996 Jul 06;348(9019):17-24.
102. Bertolli J, Pangi C, Frerichs R, Halloran ME. A case-control study of the effectiveness of BCG vaccine for preventing leprosy in Yangon, Myanmar. Int J Epidemiol. 1997 Aug;26(4):888-96.
103. Duppre NC, Camacho LA, da Cunha SS, Struchiner CJ, Sales AM, Nery JA, *et al*. Effectiveness of BCG vaccination among leprosy contacts: A cohort study. Trans R Soc Trop Med Hyg. 2008 Jul;102(7):631-8.
104. Gillini L, Cooreman E, Wood T, Pemmaraju VR, Saunderson P. Global practices in regard to implementation of preventive measures for leprosy. PLoS Negl Trop Dis. 2017 May;11(5):e0005399.