BMJ Best Practice

Leprosy

Straight to the point of care

Last updated: Nov 10, 2022

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Summary

Leprosy is a chronic infectious disease caused by the acid-fast bacteria *Mycobacterium leprae* and *M lepromatosis* , characterized by skin lesion(s) and involvement of peripheral nerves.

Skin lesions can be erythematous or hypopigmented, single or multiple macules, papules, or nodules, sometimes with loss of sensation.

Skin smear may or may not be positive for acid-fast bacilli (AFB) depending on the classification (multibacillary vs. paucibacillary).

Nerve damage to peripheral nerve trunks may occur, with loss of sensation in the skin and weakness of muscles supplied by the affected nerve, leading to disabilities.

Diagnosis is most commonly based on clinical signs and symptoms, and in practice, people usually report on their own to the health center.

The standard WHO-recommended treatment for leprosy is with multidrug therapy.

Definition

Leprosy (also known as Hansen disease) is a chronic infectious disease characterized by one or more of the following features: hypopigmented or erythematous skin lesion(s) with loss of sensation; involvement of the peripheral nerves, as demonstrated by loss of sensation, paresthesias (tingling of hands and feet), and weakness of the muscles of hands, feet, or face.[1]

THEORY

Epidemiology

Leprosy affects mainly young adults in their most productive period of life. Leprosy is a leading cause of permanent disability in the world, mainly affecting those countries situated in the tropics. In 2020, 127,558 new cases of leprosy were reported in 139 countries. Almost 7% of these cases were among children under 15 years old and 7198 of new cases had grade 2 disabilities.[6] In 2019, 79% of new cases were reported in India, Brazil, and Indonesia.[1] In the US, approximately 150 people are diagnosed with leprosy each year.[7]

Etiology

Mycobacterium leprae is an acid-fast, gram-positive bacillus and an obligate intracellular organism that has not been successfully grown in culture media. The bacillus multiplies very slowly in macrophages and Schwann cells and prefers low temperatures (27ºC to 33ºC), as occur in the skin, peripheral nerves, and upper respiratory tract. The genome of *M leprae* has been sequenced and a different species called *M lepromatosis* has been described; however, more studies are necessary to determine the clinical implications.[8] [9]

Pathophysiology

The mode of transmission is uncertain; however, entry through the respiratory route appears most probable (although other routes, particularly broken skin, cannot be ruled out).[10] [11] [12] [13]

In the southern United States, patients with leprosy and no foreign exposure have been found to be infected with the same strain of *Mycobacterium leprae* as wild armadillos in the region, suggesting zoonotic transmission.[14] *M leprae* and *M lepromatosis* have been found in red squirrels in the UK and Ireland and in wild chimpanzees in West Africa.[15] [16]

Leprosy presents as a clinical spectrum that correlates with the level of the immune response to *Mycobacterium leprae* . At one end of the spectrum, patients with tuberculoid leprosy have a localized disease and lesions are characterized by Th1 cytokines (IFN-gamma, IL-2, and TNF-beta), Th17 cells, and CD1a restricted T cells, indicative of cell-mediated immunity. At the other end of the spectrum, patients with lepromatous leprosy have a more disseminated form of the disease and the lesions are characterized by Th2 cytokines with increased humoral response and suppressed macrophage activity (IL-4, IL-5, IL-10, IL-13).[17] Type I IFN and CD4 + T regs, predominate in these patients.[18]

Most people exposed to *M leprae* do not acquire the disease, which suggests that disease development depends on immunologic, genetic, and environmental factors. Possible genetic factors include the PARK2 and PACRG genes, and genes in the NOD2 pathway. Some genes are also associated with different forms of leprosy: HLA-DR2 has been associated with the tuberculoid form, and HLA-DQ1 has been associated with the lepromatous form.[19] [20]

Classification

Ridley Jopling Classification[2]

Leprosy presents as a clinical spectrum that correlates with the level of the immune response to *Mycobacterium leprae* . At one end of the spectrum, patients with tuberculoid leprosy are resistant to the

pathogen and the infection is localized. In contrast, patients with lepromatous leprosy are more susceptible to the pathogen and the infection is systemically disseminated.

Lepromatous leprosy (LL)

- Multiple papules, plaques, or nodular lesions, symmetrical and disseminated.
- Can have absence of eyebrows and eyelashes and infiltration of the ears.
- The disease can involve mucous membranes of the mouth, nose, pharynx, larynx, trachea, eyes, testes, liver, and bones.

Borderline leprosy

- Can be unstable and move between types.
- Borderline lepromatous (BL): similar to lepromatous leprosy.
- Mid-borderline leprosy (BB): annular plaques, punched out lesions.
- Borderline tuberculoid (BT): asymmetric lesions, macules, or plaques.

Tuberculoid leprosy (TT)

- Few lesions, mostly macular with sharp margin, can be erythematous or hypopigmented. Lesions are localized and asymmetric.

Indeterminate leprosy

- This is an early phase in the natural history of leprosy. At this stage the disease has not yet determined into which type it will evolve.
- Usually presents as a single hypopigmented macule with anesthesia.

World Health Organization (WHO) Classification[3]

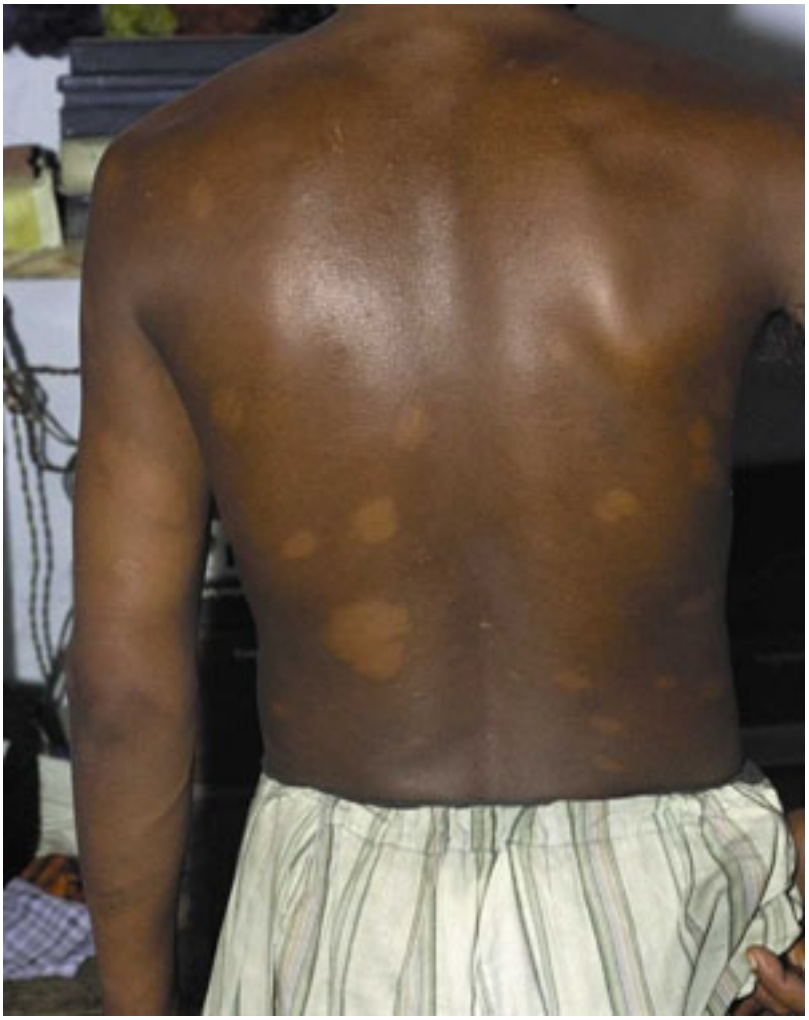
Based on the number of skin lesions. Designed to be used in areas with no access to other diagnostic methods and to serve as a basis for treatment.

- Multibacillary (MB) leprosy includes polar lepromatous (LL), borderline lepromatous (BL), and mid-borderline (BB) cases in the Ridley-Jopling classification and is defined as having 6 or more skin lesions and a positive skin smear if available.
- Paucibacillary (PB) leprosy includes indeterminate (I), polar tuberculoid (TT), and borderline tuberculoid (BT) in the Ridley-Jopling classification and is defined as having up to 5 skin lesions and a negative smear if available.

Case history

Case history #1

A 25-year-old married, male farm laborer from a village in Tanzania presents with multiple erythematous patches distributed on the trunk, back, arms, and legs, and with loss of sensation and tingling in his feet and fingers. On examination, papules and plaques of varying sizes between 0.5 and 10.0 cm are present, distributed asymmetrically, mainly over the trunk. He is not malnourished and does not have lymphadenopathy or splenomegaly. His vital signs are normal, and the genital and systemic exams are normal.



Early multibacillary (MB) leprosy

WHO

Other presentations

Two types of immunologic reactions affect 30% to 50% of patients with leprosy: type 1 reaction (reversal reaction) and type 2 reaction (erythema nodosum leprosum). In type 1 reaction, existing skin lesions become erythematous and edematous, and there may be spontaneous nerve pain, tenderness, paresthesias, and/or loss of nerve function (claw hand, foot drop, facial palsy); systemic symptoms are unusual. Type 2 reaction includes: the rapid appearance of crops of painful, erythematous subcutaneous nodules that can ulcerate; fever; malaise; anorexia; arthralgias; orchitis; epididymitis; iritis; and neuritis. These reactions are often incorrectly viewed as complications of multidrug therapy. Reactions are medical emergencies that can increase leprosy-related morbidity and it is important to specifically recognize and treat reactions, to reduce the burden of disability in leprosy. A third, relatively rare, reaction is called Lucio phenomenon. This occurs in diffuse non-nodular lepromatous leprosy (lepra bonita) and has been associated with a different species called *Mycobacterium lepromatosis* .[4] Symptoms include crops of hemorrhagic infarcts in the skin, and plaques, which become necrotic and ulcerated. Atrophic scars are left behind; systemic symptoms are unusual. Immunologic reactions can occur any time, before, during, or after treatment.[5]

Approach

In leprosy-endemic countries, diagnosis is made based on the clinical examination. However, laboratory tools are useful to confirm the diagnosis and to have an accurate classification.

History

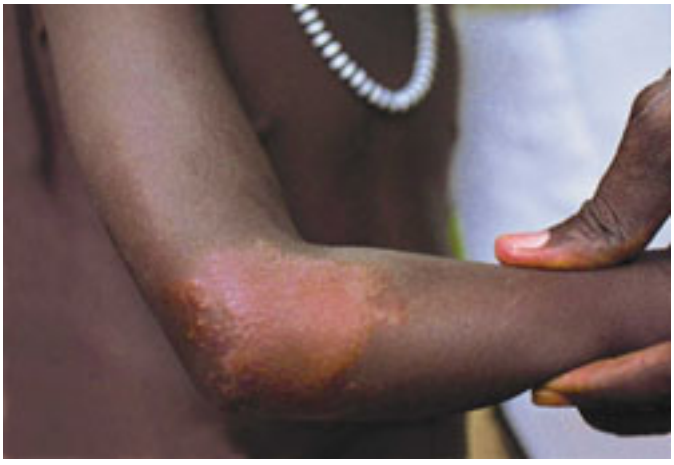
Family members with leprosy, living in an endemic country, travel history, and contact with people with untreated leprosy, are important elements to consider. The average incubation period is thought to be between 3 and 5 years, although the minimum period has been reported as being as short as a few weeks, based on the occurrence of leprosy among young infants.[31] The maximum incubation period reported is ≥30 years, as observed among war veterans known to have been exposed for short periods in endemic areas but otherwise living in nonendemic areas.

Physical exam

Skin lesions can be single or multiple and can be hypopigmented or erythematous. A variety of skin lesions may be seen, but macules, papules, or nodules are common. The disease can also occur with multiple infiltrated patches or just diffuse skin infiltration. Sensory loss is a typical feature of leprosy; the skin lesion shows loss of sensation to pinprick and/or light touch.

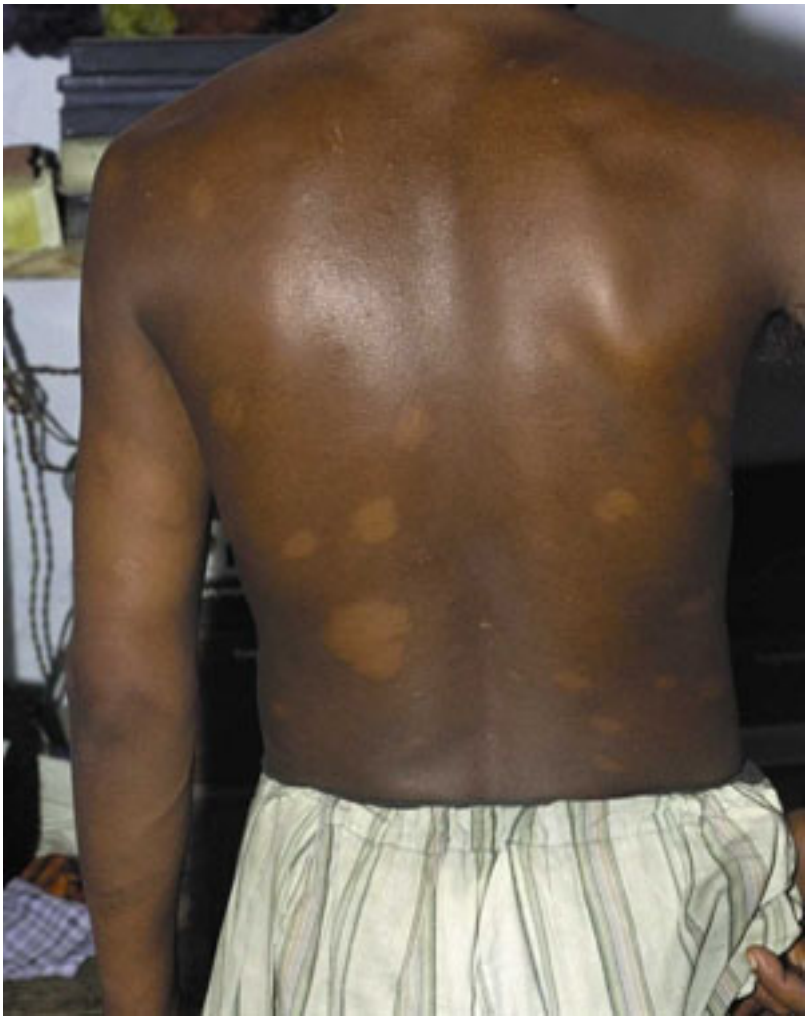
Examination should include palpation of peripheral nerves. There may be tenderness, paresthesias, or thickening of a nerve. Most commonly involved are the ulnar nerve, radial cutaneous nerve, median nerve, popliteal nerve, tibial nerve, and great auricular nerve. Numbness of extremities and loss of nerve function (as evidenced by claw hands, foot drop, facial paralysis) may also be present.

Pure neural leprosy is a rare presentation of leprosy and is found in 5% to 20% of patients.[32] Patients present with neuropathy without evidence of skin lesions.[33]



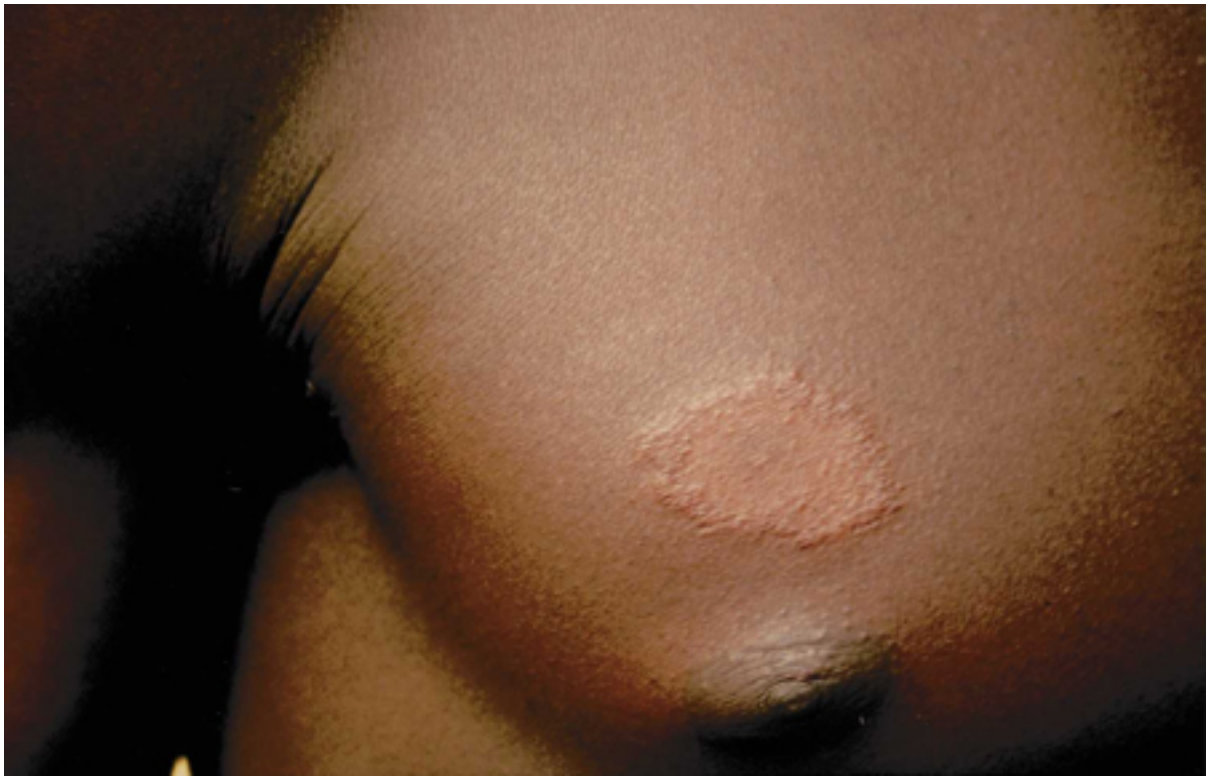
Paucibacillary (PB) leprosy (borderline tuberculoid)

WHO



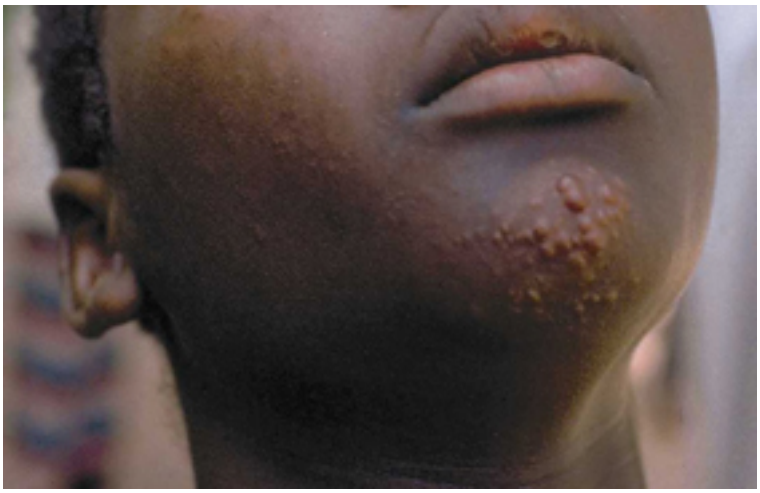
Early multibacillary (MB) leprosy

WHO



Paucibacillary (PB) leprosy: tuberculoid (TT)

WHO



Multibacillary (MB) leprosy nodules

WHO

Investigations

Slit-skin smears using Wade-Fite stain can be taken when available. Rod-shaped, red-stained leprosy bacilli can be seen in multibacillary patients. Wherever possible, histopathology by a skin biopsy can be a valuable aid to differential diagnosis and for detailed classification of the disease. Nerve biopsy may be done in cases of pure neural leprosy.

Polymerase chain reaction may be used to detect *Mycobacterium leprae* DNA in tissue. It is useful to diagnose lepromatous leprosy (LL) but less sensitive to diagnose tuberculoid leprosy (TT) or borderline tuberculoid leprosy (BT).

Immunologic reactions

Two types of reactions affect 30% to 50% of patients with leprosy: type 1 reaction (reversal reaction) and type 2 reaction (erythema nodosum leprosum). These reactions are often incorrectly viewed as complications of multidrug therapy. Reactions are medical emergencies that can increase leprosy-related morbidity and so it is important to specifically recognize and treat reactions, to reduce the burden of disability in leprosy.

A third reaction, known as Lucio phenomenon is relatively rare. Immunologic reactions can occur any time, before, during, or after treatment.[5]

Type 1 reaction (reversal reaction)

- Most commonly occurs in BT, mid-borderline leprosy (BB), borderline lepromatous (BL), LL
- Existing skin lesions become erythematous and edematous
- Systemic symptoms are unusual
- Neuritis: spontaneous nerve pain, tenderness, paresthesias, and/or loss of nerve function (as evidenced by claw hand, foot drop, facial palsy) are commonly associated.

Type 2 reaction (erythema nodosum leprosum)

- Most commonly occurs in BL and LL
- Rapid appearance of crops of painful, erythematous subcutaneous nodules that can ulcerate
- Fever, malaise, anorexia
- Arthralgias
- Orchitis, epididymitis, iritis
- Neuritis.

Lucio phenomenon

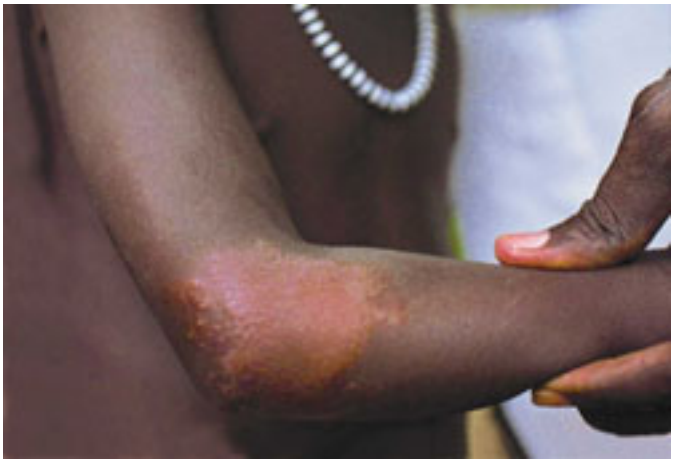
- Occurs in diffuse non-nodular lepromatous leprosy (lepra bonita); has been associated with a different species called *M lepromatosis* [4]
- Crops of hemorrhagic infarcts in the skin, plaques, which become necrotic and ulcerated
- Atrophic scars left behind
- Systemic symptoms are unusual.

History and exam

Key diagnostic factors

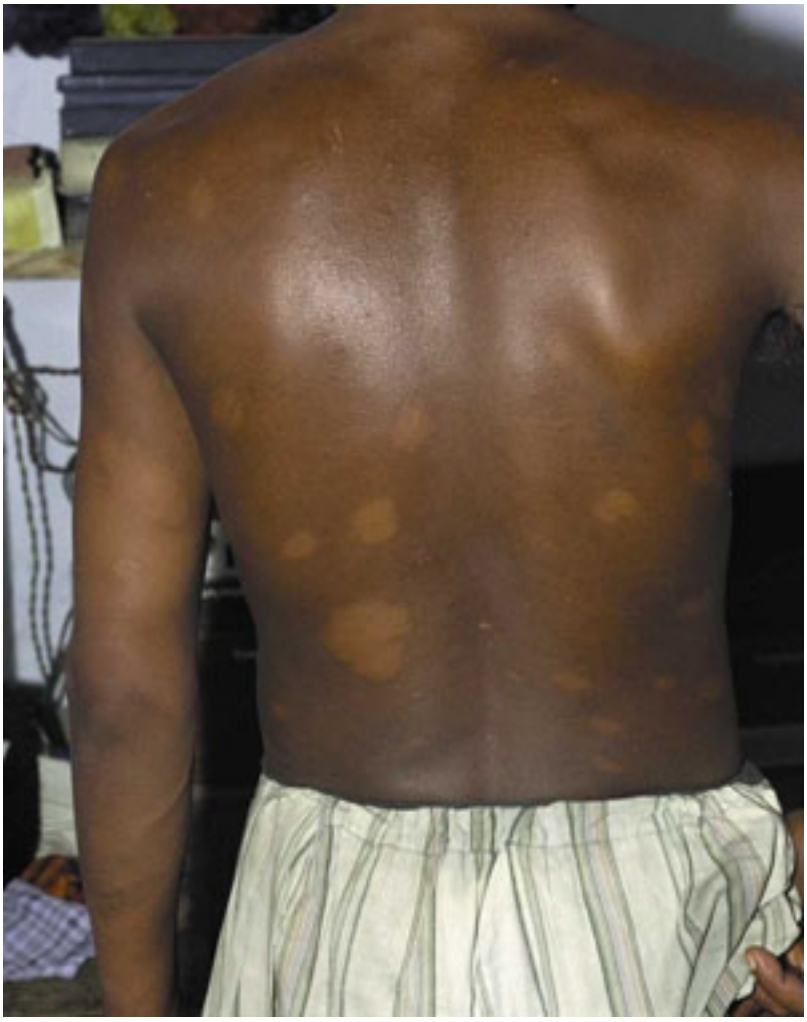
typical skin lesions (common)

- A variety may be seen, but macules, papules, or nodules are common.



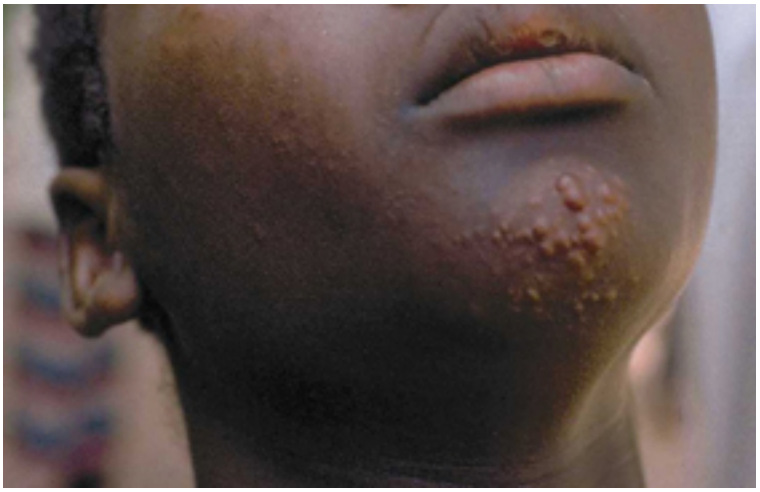
Paucibacillary (PB) leprosy (borderline tuberculoid)

WHO



Early multibacillary (MB) leprosy

WHO



Multibacillary (MB) leprosy nodules

WHO

- An early lesion may occur as an ill-defined, hypopigmented or erythematous patch with anesthesia. The lesions can be reddish or copper-colored. The disease can also occur with multiple infiltrated plaques or just diffuse skin infiltration.

nerve involvement (common)

- Examination should include palpation of peripheral nerves. There may be tenderness, paresthesias, or thickening of a nerve. Most commonly involved are the ulnar nerve, radial cutaneous nerve, median nerve, popliteal nerve, tibial nerve, and great auricular nerve. Also numbness of extremities and loss of nerve function (claw hands, foot drop, facial paralysis).
- Leprosy can manifest itself as areas of anesthesia in the skin with no skin patches (pure neural leprosy).

sensory loss (common)

- A typical feature of leprosy. Skin lesions can show loss of sensation to pinprick and/or light touch.

Other diagnostic factors

immunologic reactions (common)

- Two types of reactions affect 30% to 50% of patients with leprosy: type 1 reaction (reversal reaction) and type 2 reaction (erythema nodosum leprosum). These reactions are often incorrectly viewed as complications of multidrug therapy. Reactions are medical emergencies that can increase leprosy-related morbidity. It is important to specifically recognize and treat reactions, to reduce the burden of disability in leprosy. A third, relatively rare, reaction is called Lucio phenomenon.

eye lesions (common)

- The eye may be affected by nerve damage to the muscles of the eyelid or to the cornea. Leprosy is the third leading cause of blindness worldwide. Leprosy patients can develop ocular complications, such as corneal ulceration, iridocyclitis, and lagophthalmos.

Risk factors

Strong

close contact with a person with multibacillary leprosy

- The actual incidence among contacts and the relative risk for them appear to vary considerably in different studies. Infection rates for contacts of people with lepromatous leprosy have varied from 6.2 per 1000 per year in Cebu province in the Philippines to 55.8 per 1000 per year in a part of South India.[21] [22]

poverty

- Leprosy is usually, but not exclusively, associated with deprived communities where poor nutrition, overcrowding, and poor standards of hygiene are most common.

residence in endemic area

- In 2018, 96% of new cases of leprosy were reported in 23 global priority countries: Angola, Bangladesh, Brazil, Comoros, Côte d'Ivoire, Democratic Republic of the Congo, Egypt, Ethiopia, Micronesia (Federated States of), India, Indonesia, Kiribati, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, Philippines, South Sudan, Sri Lanka, Sudan, Somalia, and United Republic of Tanzania.[23] The majority of these cases were in Brazil, India, and Indonesia.

Weak

genetic predisposition

- There is evidence that not all people who are infected with *Mycobacterium leprae* develop leprosy. Genetic factors are thought to be influential, based on the observation of clustering of leprosy around certain families.

zoonotic transmission

- In the southern United States, patients with leprosy and no foreign exposure have been found to be infected with the same strain of *Mycobacterium leprae* as wild armadillos in the region.[14] *M leprae* and *M lepromatosis* have been found in red squirrels in the UK and Ireland and in wild chimpanzees in West Africa.[15] [16]

Investigations

1st test to order

Test	Result
skin smear • In developing countries, skin smear services are not always available, and their reliability is often doubtful. Therefore, more and more programs base their classification on clinical criteria. The essential feature is based on the number of skin lesions.	**positive for acid-fast bacilli (AFB, Fite or Wade stain)**
skin and/or nerve biopsy and histopathology • Wherever possible, histopathology can be a valuable aid to differential diagnosis and for accurate classification of the disease. • Different forms of leprosy are accompanied by specific histopathologic pictures: toward the tuberculoid (TT) end of the spectrum, histopathology shows epithelioid cells, well-defined granulomas, Langhans giant cells, and lymphocytes with negative Wade-Fite staining; while toward the lepromatous (LL) end of the spectrum, there are more foamy macrophages and Wade-Fite staining shows mycobacteria. • Nerve biopsy may be done in cases of pure neural leprosy.	**helps determine classification of the disease and presence of acid-fast bacilli (AFB)**

Other tests to consider

Test	Result
polymerase chain reaction • Detects *Mycobacterium leprae* DNA in tissue. Useful to diagnose lepromatous leprosy (LL) but less sensitive to diagnose tuberculoid (TT) or borderline tuberculoid (BT), where the diagnosis is more difficult. Not available in all settings.	**detection of *M leprae* or *M lepromatosis* DNA**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Psoriasis	• Presents with widespread scaly plaques of the skin, especially on the extensor aspects of joints. May be involvement of the nails and arthritis. • There is no neural involvement, and skin nodules are not found.	• Diagnosis is usually based on the appearance of the skin. There are no special blood tests or diagnostic procedures but a skin biopsy may be needed to rule out other disorders and to confirm the diagnosis. • Skin biopsy histology shows acanthosis of the epithelium, absence of granulomas, but focal accumulation of lymphocytes and neutrophils. No acid-fast-bacilli (AFB) are present in the biopsy.
Eczema	• Features widespread dryness of the skin and recurring skin rashes with erythema or pruritus. • Areas of temporary skin discoloration may appear. • Likely to be found on the flexor aspect of joints. May be a history of allergy. There is no neural involvement, and skin nodules are not found.	• Skin biopsy and histopathology show spongiosis, but no granulomas. • Skin testing (patch testing) may be diagnostic in allergic eczema, and CBC may show peripheral eosinophilia. No acid-fast bacilli (AFB) are present in the biopsy.
Tinea corporis	• Annular lesions with active and scaly border. There is no neural involvement, and skin nodules are not found.	• Scraping and KOH are positive. No acid-fast bacilli (AFB) are present in the biopsy.
Scars/keloids	• Burns and other injuries may leave behind anesthetic scars. There is a history of trauma or burn. There is no neural involvement, and skin nodules are not found.	• Skin biopsy and histopathology show an increase in collagen within the dermis without inflammation or granuloma formation. No acid-fast bacilli (AFB) are present.
Syphilis	• Syphilitic skin lesions may resemble the maculae of leprosy, but the absence of sensory changes and reaction to treatment are sufficiently distinctive.	• The infectious organism is *Treponema pallidum* . Skin biopsy and histopathology may show inflammatory changes, depending on the stage at presentation. Secondary syphilis may be associated with granuloma formation, but no acid-fast

Condition	Differentiating signs / symptoms	Differentiating tests
		bacilli (AFB) are present on special stains. • The venereal disease research lab (VDRL) reaction alone cannot always be depended on in differential diagnosis, as false-positive reactions are not uncommon in borderline lepromatous and lepromatous leprosy, in which case confirmatory tests such as FTA-ABS are necessary. • Examination of skin scrapings or skin biopsy with dark field microscopy may visualize the spirochetes.
Systemic lupus erythematosus	• Skin lesions can be annular with raised border and central clearing similar to borderline leprosy.	• Positive antinuclear antibodies (ANA). Patients with leprosy often have false positive ANA, in which case specific antibodies to dsDNA may differentiate.
Mycosis fungoides	• Early lesions might be mistaken for nodular leprosy. Late-stage disease may have systemic involvement.	• Skin biopsy and histopathology are diagnostic, with infiltrates of atypical lymphocytes and clonality on T-cell gene re-arrangement studies.
Lupus vulgaris	• Highly likely to be mistaken for leprosy lesions, and in both diseases acid-fast bacilli are difficult to demonstrate. Lupus produces painful, ulcerating skin lesions around the mouth, eyes, nose, and ears. There is a greater tendency to scar formation, and there are no sensory changes.	• Skin biopsy will show granulomatous inflammation and, occasionally, caseous necrosis with *Mycobacterium tuberculosis* acid-fast bacilli (AFB) on special stains. Distinction from leprosy is difficult, but in cutaneous tuberculosis, *M tuberculosis* can be grown in culture or demonstrated with polymerase chain reaction.
Cutaneous leishmaniasis	• Cutaneous leishmaniasis may be mistaken for leprosy. Papular lesions become ulcerated. Anergic leishmaniasis can resemble lepromatous leprosy.	• Skin scraping, and histopathology. Leishmania can be grown in culture (NNN media) or demonstrated by polymerase chain reaction.

Approach

Early diagnosis and treatment with multidrug therapy (MDT) remains the single most important element in curing the disease, preventing disabilities, and possibly reducing transmission.

Multidrug therapy: general principles

MDT was developed because of the widespread emergence of dapsone resistance, and the regimens were designed on the principle that they would effectively prevent development of resistance to any single drug used in the combination.[34] [35]

- The World Health Organization (WHO) recommends the same three-drug regimen for all patients with leprosy, regardless of whether they have multibacillary (MB) leprosy (≥6 lesions) or paucibacillary (PB) leprosy (1-5 lesions). MDT blister calendar packs contain rifampin, dapsone, and clofazimine. The only difference is that patients with PB leprosy are treated for at least 6 months, while patients with MB leprosy are treated for at least 12 months.[34]
- Patients who cannot take one of the first-line drugs because of adverse effects, contraindications, or intercurrent diseases can replace them with a fluoroquinolone (e.g., ofloxacin, levofloxacin, moxifloxacin), or minocycline, or clarithromycin as part of the multidrug regimen.[36] Fluoroquinolones have been associated with adverse effects including tendonitis, tendon rupture, arthralgia, neuropathies, other musculoskeletal or nervous system effects, aortic dissection, significant hypoglycemia, and mental health adverse effects.[37] [38] [39]
- In the case of rifampin-resistant leprosy, the WHO recommends the use of two second-line drugs - a fluoroquinolone (e.g., ofloxacin, levofloxacin, moxifloxacin), or minocycline, or clarithromycin - for 6 months, followed by one second-line drug for an additional 18 months. This should be given in addition to clofazimine for the whole duration of treatment. In the case of resistance to both rifampin and a fluoroquinolone, patients may be treated with clarithromycin and minocycline for 6 months, followed by either clarithromycin or minocycline for an additional 18 months, in addition to clofazimine for the whole duration of treatment.[34]

Rifampin:

- Standard monthly dose has proved relatively nontoxic.
- Occasional cases of renal failure, thrombocytopenia, influenza-like syndrome, and hepatitis have been reported.
- Highly bactericidal.
- Drug resistance is low if combined with dapsone.

Clofazimine:

- Virtually nontoxic in the dosage employed for MB leprosy.
- Pigmentation of the skin, particularly within skin lesions, is common, but it clears completely within 6 to 12 months after treatment is discontinued.
- In higher doses it may occasionally produce severe gastrointestinal adverse effects.

Dapsone:

- Relatively nontoxic in the doses used.
- Occasional cases of delayed hypersensitivity reactions and, less commonly, agranulocytosis.

- Screening for HLA-B*13:01 before treatment may reduce incidence of dapsone hypersensitivity syndrome in high risk populations.[40]
- Mild hemolytic anemia is common following treatment with the drug.
- Severe hemolytic anemia is rare except in patients with glucose-6-phosphate dehydrogenase deficiency.
- Drug resistance is low if combined with rifampin.

WHO treatment guidelines have been followed here for the treatment of adult patients.

Treatment of immunologic reactions

Two types of reactions affect 30% to 50% of patients with leprosy: type 1 reaction (reversal reaction) and type 2 reaction (erythema nodosum leprosum). These reactions are often incorrectly viewed as complications of multidrug therapy. Reactions are medical emergencies that can increase leprosy-related morbidity and so it is important to specifically recognize and treat reactions, to reduce the burden of disability in leprosy.[41] A third reaction, known as Lucio phenomenon, is relatively rare. Immunologic reactions can occur any time, before, during, or after treatment.[5] [35]

Type 1 reaction (reversal reaction):

- Prednisone provides rapid symptomatic relief and helps reverse nerve function impairment. The regimen must be tailored individually based on whether nerve tenderness and motor or sensory deficits are present. Symptoms should be reassessed every 2 weeks. If nerve function improves, the dose can be reduced slowly during the next 3 months.[42]
- Long-term corticosteroid use carries risk of adverse effects, prompting exploration of corticosteroid-sparing agents, such as methotrexate or cyclosporine.[43] Methotrexate or cyclosporine monotherapy may be an alternative option.[41]

Type 2 reaction (erythema nodosum leprosum):

- The current treatment of choice, thalidomide, is extremely effective at improving symptoms. However, given its teratogenicity, thalidomide is avoided in women of childbearing potential. Treatment of this particular population remains a challenge. Prednisone can be used. Long-term corticosteroid use carries the risk of adverse effects, prompting exploration of corticosteroid-sparing agents, such as methotrexate.[43]
- While the combination of thalidomide and prednisone is approved for the treatment of erythema nodosum leprosum plus neuritis, it should be avoided because of the increased risk of deep vein thrombosis. Higher doses of clofazimine as part of the multidrug regimen can be an option for those who cannot receive thalidomide, but its full effect is not observed until 4 to 6 weeks from initiation.
- Methotrexate monotherapy may be an alternative option.[41]

Lucio phenomenon

- If not already on MDT, patients should be started on medications for lepromatous leprosy, including rifampin, dapsone, and clofazimine. In addition, corticosteroids should be initiated and tapered over months.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
multibacillary (MB) or paucibacillary (PB): no rifampin or fluoroquinolone resistance		
	1st	WHO standard multidrug therapy: triple drug regimen
	2nd	alternative antibiotic regimen as part of multidrug therapy regimen
multibacillary (MB) or paucibacillary (PB): rifampin ± fluoroquinolone resistance		
	1st	WHO alternative multidrug therapy: triple drug regimen

Ongoing (summary)		
type 1 reaction (reversal reaction)		
	1st	prednisone plus continued multidrug therapy
	adjunct	cyclosporine or methotrexate
type 2 reaction (erythema nodosum leprosum)		
	1st	thalidomide or prednisone or clofazimine or methotrexate plus continued multidrug therapy
Lucio phenomenon		
	1st	prednisone plus multidrug therapy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

multibacillary (MB) or paucibacillary (PB): no rifampin or fluoroquinolone resistance

1st **WHO standard multidrug therapy: triple drug regimen**

Primary options

» rifampin: 600 mg orally once monthly
-and-
» clofazimine: 50 mg orally once daily plus an additional 300 mg once monthly
-and-
» dapsone: 100 mg orally once daily

» WHO recommends the same three-drug regimen for all leprosy patients, regardless of whether they have MB leprosy (≥6 lesions) or PB leprosy (1-5 lesions). Multidrug therapy blister calendar packs contain rifampin, dapsone, and clofazimine. The only difference is that patients with PB leprosy are treated for at least 6 months, while patients with MB leprosy are treated for at least 12 months.[34]

» Infectiousness becomes negligible after starting therapy containing rifampin.[30]

» If toxic effects or resistance occur, an alternative regimen should be used. Dapsone should be stopped if severe toxic effects occur; no further modification required.

2nd **alternative antibiotic regimen as part of multidrug therapy regimen**

Primary options

» minocycline: 100 mg orally once daily

OR

» clarithromycin: 500 mg orally once daily

OR

» ofloxacin: 400 mg orally once daily

OR

» levofloxacin: 500 mg orally once daily

Acute

OR

» moxifloxacin: 400 mg orally once daily

» Patients who cannot take one of the first-line drugs because of adverse effects, contraindications, or intercurrent diseases can replace them with a fluoroquinolone (e.g., ofloxacin, levofloxacin, moxifloxacin), or minocycline, or clarithromycin as part of the multidrug regimen.[34] [44] [45] [46]

» Fluoroquinolones have been associated with adverse effects including tendonitis, tendon rupture, arthralgia, neuropathies, other musculoskeletal or nervous system effects, aortic dissection, significant hypoglycemia, and mental health adverse effects.[37] [38] [39]

multibacillary (MB) or paucibacillary (PB): rifampin ± fluoroquinolone resistance

1st **WHO alternative multidrug therapy: triple drug regimen**

Primary options

» minocycline: 100 mg orally once daily
-or-
» clarithromycin: 500 mg orally once daily
-or-
» ofloxacin: 400 mg orally once daily
-or-
» levofloxacin: 500 mg orally once daily
-or-
» moxifloxacin: 400 mg orally once daily
--AND--
» clofazimine: 50 mg orally once daily

» In the case of rifampin-resistant leprosy, the WHO recommends the use of two second-line drugs - a fluoroquinolone (e.g., ofloxacin, levofloxacin, moxifloxacin), or minocycline, or clarithromycin - for 6 months, followed by one second-line drug for an additional 18 months. This should be given in addition to clofazimine for the whole duration of treatment.[34]

» In the case of resistance to both rifampin and a fluoroquinolone, patients may be treated with clarithromycin and minocycline for 6 months, followed by either clarithromycin or minocycline for an additional 18 months, in addition to clofazimine for the whole duration of treatment.[34]

Acute

» Fluoroquinolones have been associated with adverse effects including tendonitis, tendon rupture, arthralgia, neuropathies, other musculoskeletal or nervous system effects, aortic dissection, significant hypoglycemia, and mental health adverse effects.[37] [38] [39]

Ongoing

type 1 reaction (reversal reaction)

1st **prednisone plus continued multidrug therapy**

Primary options

» prednisone: 0.5 to 1 mg/kg orally once daily

» Type 1 reaction (reversal reaction) is a medical emergency that can increase leprosy-related morbidity. It is important that it is recognized and treated to reduce the burden of disability in leprosy. It is seen most frequently in patients with borderline tuberculoid (BT), mid-borderline leprosy (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). Existing skin lesions become erythematous and edematous. Spontaneous nerve pain, tenderness, paresthesias, and/or loss of nerve function (claw hand, foot drop, facial palsy) are commonly associated with it. Systemic symptoms are unusual. It is often incorrectly viewed as a complication of multidrug therapy.

» Prednisone provides rapid symptomatic relief and helps reverse nerve function impairment. The regimen must be tailored individually based on whether nerve tenderness and motor or sensory deficits are present. Symptoms should be reassessed every 2 weeks. If nerve function improves, the dose can be reduced slowly over the next 3 months.[42]

adjunct **cyclosporine or methotrexate**

Treatment recommended for SOME patients in selected patient group

Primary options

» cyclosporine non-modified: consult specialist for guidance on dose

OR

» methotrexate: consult specialist for guidance on dose

» Long-term corticosteroid use carries the risk of adverse effects, prompting the use of corticosteroid-sparing agents, such as methotrexate or cyclosporine.[43] Methotrexate or cyclosporine monotherapy may be an alternative option.[41]

type 2 reaction (erythema nodosum leprosum)

Ongoing

1st **thalidomide or prednisone or clofazimine or methotrexate plus continued multidrug therapy**

Primary options

» thalidomide: 100-400 mg orally once daily

Secondary options

» prednisone: 0.5 to 1 mg/kg orally once daily

OR

» prednisone: 0.5 to 1 mg/kg orally once daily
-and-
» methotrexate: consult specialist for guidance on dose

Tertiary options

» clofazimine: 300 mg orally once daily for 1 month, tapered to 100 mg orally once daily over the next 12 months as part of a multidrug regimen

OR

» methotrexate: consult specialist for guidance on dose

» Type 2 reaction (erythema nodosum leprosum) is a medical emergency that can increase leprosy-related morbidity. It is important that it is recognized and treated to reduce the burden of disability in leprosy. It is seen most frequently in patients with BL and LL. It is characterized by the rapid appearance of crops of painful, erythematous subcutaneous nodules, which can ulcerate. Neuritis may develop. Systemic features are common (fever, malaise, anorexia) as are arthralgias, orchitis, epididymitis, and iritis. It is often incorrectly viewed as a complication of multidrug therapy.

» The current treatment of choice, thalidomide, is extremely effective at improving symptoms. However given its teratogenicity, thalidomide is avoided in women of childbearing potential. Treatment of this particular population remains a challenge. Prednisone can be used instead. Long-term corticosteroid use carries the risk of adverse effects, prompting the use of corticosteroid-sparing agents, such as methotrexate.[43] While the combination of thalidomide and prednisone is approved for the treatment of erythema nodosum leprosum plus

Ongoing

neuritis, it should be avoided because of the increased risk of deep vein thrombosis.

» Increased doses of clofazimine as part of the multidrug regimen can be an option for those who cannot receive thalidomide, but its full effect is not observed until 4 to 6 weeks from initiation.

» Methotrexate monotherapy may be an alternative option.[41]

Lucio phenomenon

1st **prednisone plus multidrug therapy**

Primary options

» prednisone: 0.5 to 1 mg/kg orally once daily

» Lucio phenomenon is a relatively rare immunologic reaction. It occurs in diffuse non-nodular lepromatous leprosy (lepra bonita). It has been associated with a different species, *Mycobacterium lepromatosis* .[4] It is characterized by crops of hemorrhagic skin infarcts and plaques that become necrotic and ulcerated, leaving behind atrophic scars. Systemic symptoms are unusual.

» If not already on multidrug therapy, patients should be started on medications for lepromatous leprosy. In addition, corticosteroids should be initiated and tapered over months.

Emerging

Mycobacterium leprae-bactericidal antibiotics

Two antibiotics have shown to be highly bactericidal against *M leprae* , and could potentially be included in the multidrug therapy regimen. These antibiotics are rifapentine, a long-acting rifamycin derivative, and diarylquinoline (R207910).[47] [48] [49] [50]

Single-dose chemotherapy

Single-dose chemotherapy with ROM (rifampin, ofloxacin, and minocycline) has shown promising preliminary results in paucibacillary leprosy patients with a single lesion.[45] However, further studies are needed.

Primary prevention

Protection against leprosy by BCG vaccination was demonstrated in 5 large field trials conducted in India, Malawi, Myanmar, Papua New Guinea, and Uganda, although the protective effect varied from 20% to 30% in Myanmar and India to 80% in Uganda. In some studies the observed protective effect of BCG was significantly greater among individuals vaccinated at <15 years of age. The results of vaccine trials conducted in India, Malawi, and Venezuela demonstrated a protective effect against leprosy by BCG of around 50%, and second or repeated doses of BCG offered additional protection. However, the addition of killed *Mycobacterium leprae* did not improve the protection afforded by BCG vaccination.[24] [25] [26] [27]

Single-dose rifampin has been shown to be effective in reducing the incidence of leprosy in contacts. However, chemoprophylaxis is not recommended outside endemic countries.[28] All contacts should be screened every year for a period of 5 years.[29]

After diagnosis, isolation is not required. The most important measure is treatment, as infectiousness becomes negligible after starting therapy containing rifampin.[30]

Secondary prevention

If disabilities exist, patients should be advised on how to protect themselves from injuries.

Part of the WHO global strategy is to reduce new cases with visible deformity and disability; also key is the reduction of discrimination and stigma.[1]

Patient discussions

Patients should be asked to return for medical assessment and treatment if they find a new skin patch.

[CDC: Hansen's disease (leprosy)] (https://www.cdc.gov/leprosy)

FOLLOW UP

Monitoring

Monitoring

Patients should be followed up every 3 months during therapy, with evaluation of the skin and peripheral nerves. Patients should be instructed to return to the clinic earlier if signs of neuritis or reaction develop.

Patients should be educated in the prevention of injuries, and protection of hands and feet is especially important if they have loss of sensation in the extremities. Regular examination of the eyes is also important.

If the patient has developed an immunologic reaction and is being treated with prednisone or thalidomide, close follow-up is needed every month.

After completing treatment, paucibacillary leprosy patients should be followed up annually for 3 years and multibacillary patients should be followed up annually for 5 years.

Complications

Complications	Timeframe	Likelihood
paralytic disabilities	**variable**	**medium**
The common paralytic disabilities in leprosy are claw hand, foot drop, lagophthalmos, and wrist-drop. Sensory loss over the extremities leads to misuse of the affected limb, with resultant ulceration and infection and, ultimately, severe deformities and disabilities. Most of the disabilities occur before a patient is diagnosed. Therefore, the most cost-effective method to prevent disabilities is early detection and prompt treatment with multidrug therapy, including proper management of neuritis associated with leprosy reactions.[52]		
corneal ulceration, iridocyclitis, and lagophthalmos	**variable**	**low**
The eye may be damaged by direct bacillary invasion or by nerve damage. People with leprosy may develop ocular complications, such as corneal ulceration, iridocyclitis, and lagophthalmos. Corneal ulceration may result from corneal anesthesia or from paralysis of the eyelids. Iridocyclitis is one of the most important causes of blindness in leprosy and therefore should be treated promptly with mydriatics and anti-inflammatory drugs. Patients with lagophthalmos must protect their eyes by use of goggles or sunglasses. Frequent use of artificial tear drops during the day and ointments or oily drops at night is advocated.		
lymphadenopathy	**variable**	**low**
Lymph glands may be enlarged and painless with the consistency of soft rubber, particularly the femoral, inguinal, and epitrochlear glands, but occasionally one or more glands become very swollen and tender as part of a reactional state.		
hepatosplenomegaly	**variable**	**low**
The reticuloendothelial elements of the abdominal viscera are invaded by bacilli, especially in the spleen and liver, and the red marrow is similarly invaded.		
lymphedema	**variable**	**low**
Lymphedema of the lower legs may occur, giving rise to elephantiasis in neglected cases.		
kidney damage	**variable**	**low**
Glomerulonephritis, interstitial nephritis, and pyelonephritis may occur. Renal amyloidosis is a prevalent complication in some geographic areas but is uncommon in others; it appears to be related to the severity and frequency of erythema nodosum leprosum.		

Prognosis

Relapse following multidrug therapy (MDT) is very rare; in one study, the cumulative risk of relapse was 2.24%.[51] Patients are asked to return to the health center if they find a new skin patch. All *Mycobacterium*

leprae from patients who relapse remain susceptible to rifampin and clofazimine and respond favorably to a second course of MDT.

Diagnostic guidelines

International

Guidelines for the diagnosis, treatment and prevention of leprosy (https://www.who.int/publications/i/item/9789290226383) [34]

Published by: World Health Organization **Last published:** 2018

Treatment guidelines

International

Towards zero leprosy. Global leprosy (Hansen's Disease) strategy 2021-2030 (https://www.who.int/publications/i/item/978929022850) [1]

Published by: World Health Organization **Last published:** 2021

Leprosy/Hansen disease: management of reactions and prevention of disabilities (https://www.who.int/publications/i/item/9789290227595) [41]

Published by: World Health Organization **Last published:** 2020

Leprosy/Hansen disease: contact tracing and post-exposure prophylaxis (https://apps.who.int/iris/handle/10665/336679) [29]

Published by: World Health Organization **Last published:** 2020

Guidelines for the diagnosis, treatment and prevention of leprosy (https://www.who.int/publications/i/item/9789290226383) [34]

Published by: World Health Organization **Last published:** 2018

Online resources

1. CDC: Hansen's disease (leprosy) (https://www.cdc.gov/leprosy) *(external link)*

Key articles

- World Health Organization. Towards zero leprosy. Global leprosy (Hansen's Disease) strategy 2021-2030. Apr 2021 [internet publication]. Full text (https://www.who.int/publications/i/item/9789290228509)
- World Health Organization. Implementation of MDT. In: Multidrug therapy against leprosy: development and implementation over the past 25 years. Geneva: World Health Organization; 2004:45-68. Full text (http://www.who.int/entity/lep/resources/MDT03.pdf)
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- World Health Organization. Leprosy/Hansen disease: management of reactions and prevention of disabilities. 2020 [internet publication]. Full text (https://www.who.int/publications/i/item/9789290227595)

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Images

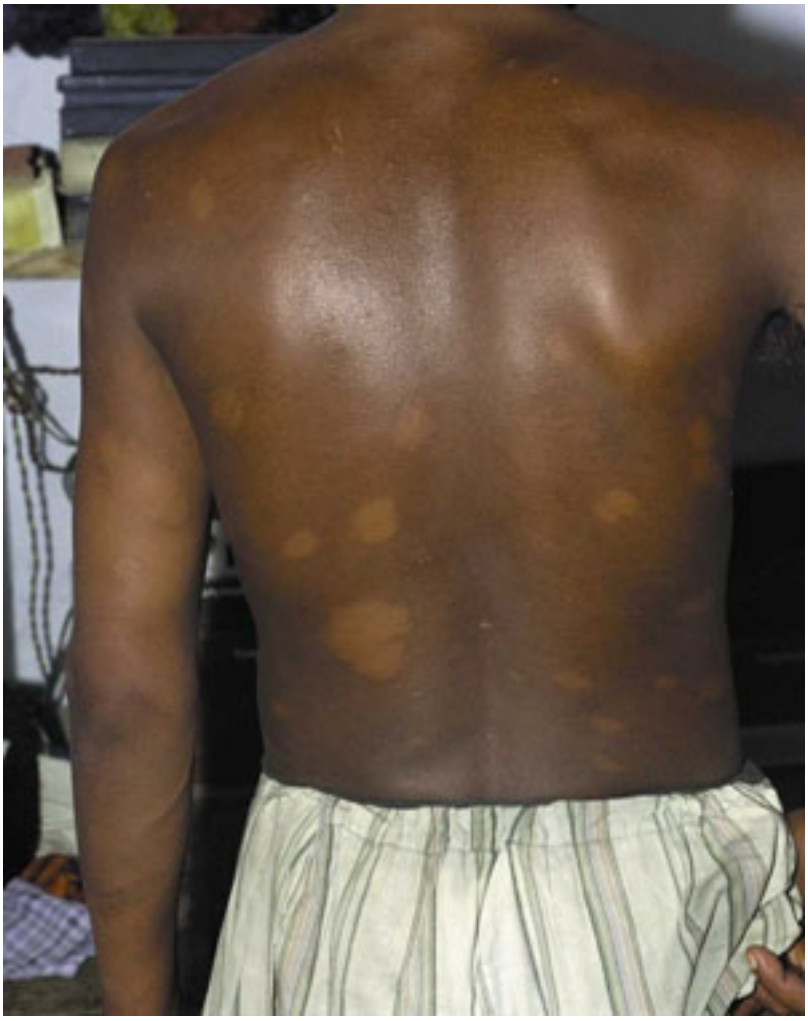

Figure 1: Early multibacillary (MB) leprosy

WHO

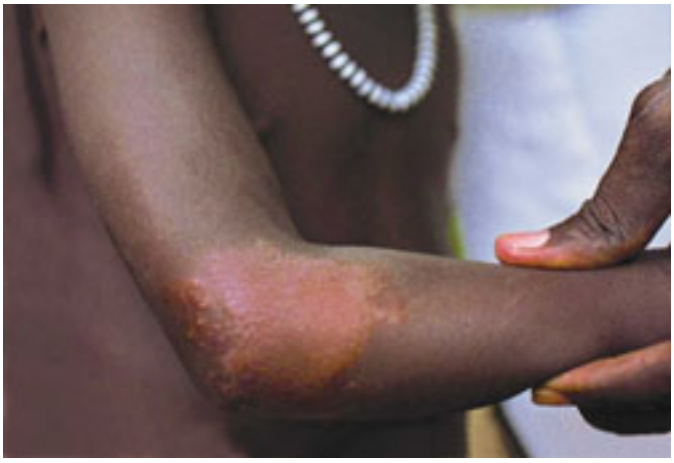

Figure 2: Paucibacillary (PB) leprosy (borderline tuberculoid)

WHO

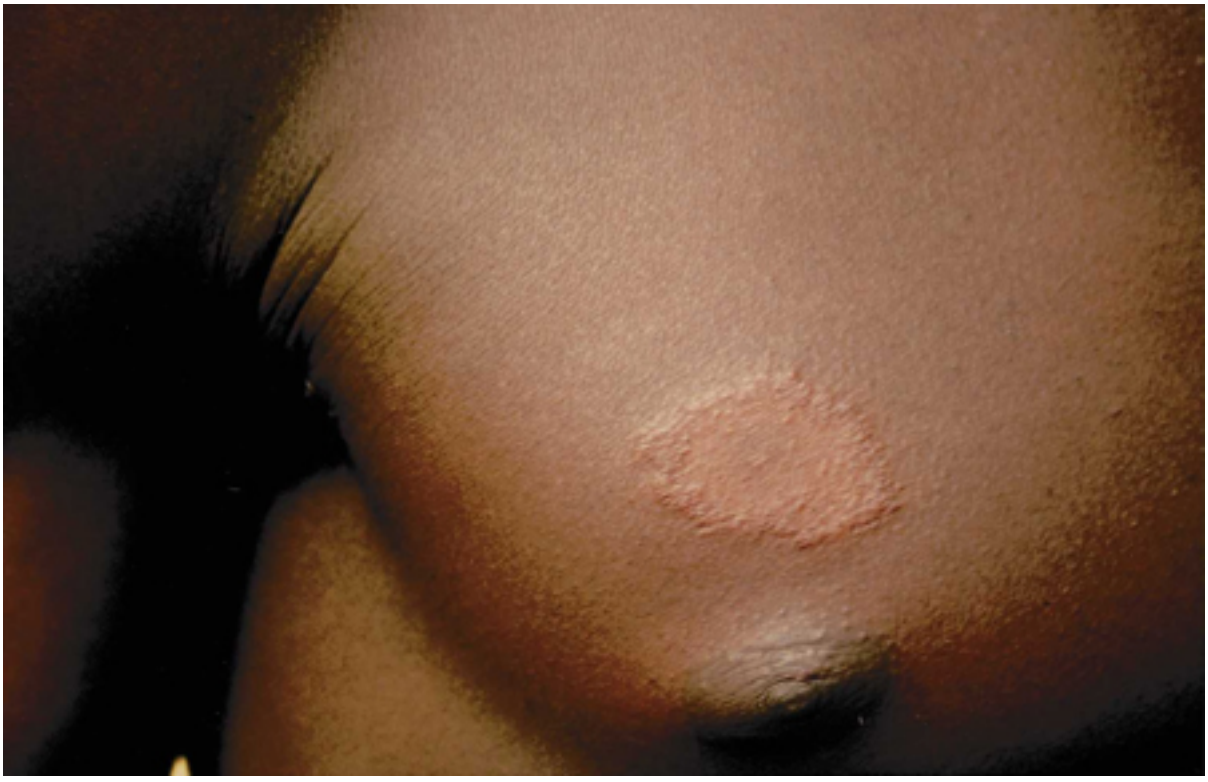

Figure 3: Paucibacillary (PB) leprosy: tuberculoid (TT)

WHO

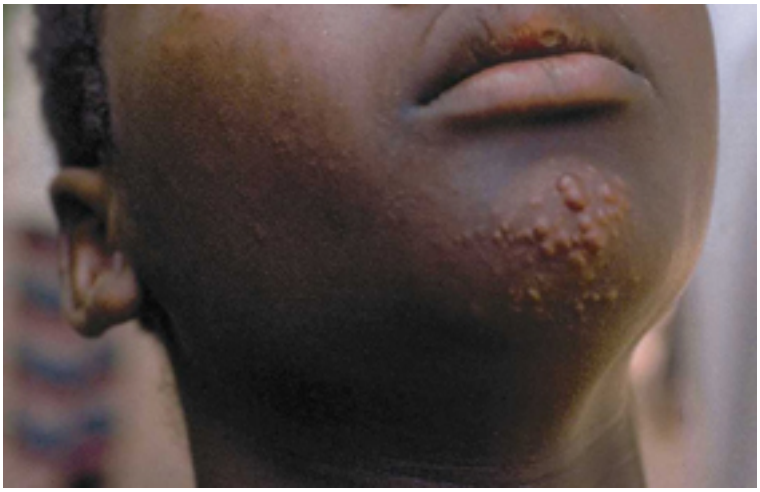

Figure 4: Multibacillary (MB) leprosy nodules

WHO

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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// Acknowledgements:

Dr Maria T. Ochoa would like to gratefully acknowledge Dr Denis Paul Jacques Daumerie, a previous contributor to this topic. DPJD declares that he has no competing interests.

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