Chapter 6
Treatment of Leprosy and Lepra Reactions

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Abstract Treatment of leprosy had undergone a significant transformation from a historical regime containing chaulmoogra oil to two decades of dapsone monotherapy from the 1940s to 1960s. Discovery of sterilizing capacities of rifampicin and the need for a multidrug regimen amid rising primary dapsone resistance led to the implementation of multidrug therapy (MDT) advocated by the World Health Organization (WHO) in 1982. WHO MDT has been the most effective tool in reducing the burden of disease globally and has remained the cornerstone of leprosy therapy till now. However, apart from changes in the duration of WHO MDT regimen, there has not been much innovation. The chapter provides a broad outline of various MDT regimens, their advantages and disadvantages, and newly introduced drug regimens along with an insight into MDT regimen for leprosy in special scenarios.

Keywords Leprosy · Multidrug therapy · Paucibacillary · Multibacillary

Introduction

Leprosy, one of the oldest infectious diseases known to mankind, was first identified by Gerhard Armauer Hansen of Norway in 1873 [1]. Apart from other organs involved, it mainly affects the skin and peripheral nerves. The world has been through the rise and fall of leprosy until it reached the stage of elimination in the twentieth century. From the late nineteenth century until 1940, chaulmoogra oil extracted from *Hydnocarpus wightiana* seeds was considered the only effective way to treat leprosy [2]. Promin was the first sulfone drug used in the treatment of leprosy in 1941. Later on, Lowe and Smith, in 1949 [3], reported the successful use of oral dapsone in the treatment of leprosy, after which dapsone monotherapy became the mainstay of treatment till the 1980s.

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Historical Regimes

Dapsone Monotherapy

GH Faget at Carville, Louisiana, was the pioneer to use dapsone for the treatment of leprosy [4]. He used promin, a derivative of dapsone via an intravenous route at a dose of 2.5 g daily [5]. Later on in 1947, dapsone itself was used for the first time by Cochrane via subcutaneous route [6]. Finally, in the 1950s, oral dapsone at a dose of 100 mg daily became the mainstay of treatment.

From 1943 until 1982, the standard treatment for lepromatous leprosy was lifelong dapsone monotherapy. Though lepromatous leprosy has the highest bacterial burden of all human diseases along with an impairment in protective cellular immunity, dapsone monotherapy proved effective despite being a bacteriostatic drug. Easy availability, cost-effectiveness, administration by oral route, and better safety profile promoted its use as monotherapy for such a long-standing period.

However, in 1964, the first case of dapsone resistance came into light due to point mutations in folP1 gene, which encodes dihydropteroate synthase [7]. Primary resistance was found in patients never put through dapsone, and secondary resistance or recurrence was identified in those previously treated with dapsone. Its use as monotherapy led to the gradual elimination of drug susceptible organisms and mutants resistant to other antimicrobials, but the dapsone-resistant mutants survived and multiplied selectively, eventually causing relapse [8].

Rifampicin Monotherapy

Rifampicin, an ansamycin, was first introduced for the treatment of leprosy in 1970 by Rees et al. [9] It targets the β-subunit of the RNA polymerase encoded by rpoB gene and blocks RNA synthesis in mycobacteria [10]. It has potent antimycobacterial activity with an ability to kill around 99% of bacilli with a single dose of 1500 mg or 3–4 daily doses of 600 mg as tested in mouse footpad [8]. This great bactericidal property due to its capability to kill intracellular bacilli along with its promising action against dapsone-resistant organisms gave it an added advantage for the treatment of this chronic infectious disease.

However, there were some challenges with the use of rifampicin, namely, its higher cost and lack of any consensus regarding the optimal dose and duration of treatment. As dapsone resistance had already become a global issue during the 1970s, similar resistance to rifampicin emerged soon due to resistance against rpoB gene [11]. These challenges were overcome when it became clear that a combination of several active drugs would be needed to maintain the efficacy of any drug regimen. The introduction of multidrug therapy (MDT) in leprosy in the 1980s was a turning point for the treatment of this stigmatized disease.

WHO MDT (WHO Multidrug Therapy)

The World Health Organization Executive Board assessed and countersigned the reports of the "Study Group on Chemotherapy of Leprosy for Control Program" on 17 May 1982, and finally the multidrug therapy came into force in 1983 [12].

MDT was introduced to address the issue of drug resistance and side effects due to prolonged use of monotherapy in addition to enhancing the effectiveness of treatment. This idea was based on the calculation that an untreated lepromatous leprosy patient carries about 11 logs of live bacilli and the proportion of the drug-resistant mutants that are expected to be occurring is estimated as 1 in 7 logs for rifampicin and 1 in 6 for dapsone and clofazimine, respectively [13]. The organisms resistant to one drug will be susceptible to the other drugs in MDT, because their mechanisms of action are different. Therefore a cocktail of several active drugs was developed as the probability of emergence of mutant resistance to any 2 drugs decreases to 1 in 13 logs, which is insignificant [13].

Since its inception in 1982, WHO MDT has undergone minor changes mainly with regard to its classification and the duration of treatment. Its evolution is highlighted in Table 6.1 [14].

Table 6.1 Evolution of MDT regimens and classification of paucibacillary and multibacillary leprosy

Year	WHO classification	WHO MDT regimens
1982 (WHO MDT)	PB: BI $< 2+$ MB: BI $\geq 2+$	PB: Rifampicin 600 mg once a month (supervised) + dapsone 100 mg daily (self-administered) for 6 months MB: Rifampicin 600 mg once a month (supervised) + dapsone 100 mg daily (self-administered) + clofazimine 300 mg once a month (supervised) and 50 mg daily (self-administered) for 2 years or till smear negativity whichever is later
1988 (WHO MDT) modified	PB: BI = 0 MB: BI $\geq 1+$	
1994 (FD-MDT 24)	PB: BI = 0 MB: BI $\geq 1+$	PB: Same as above MB: Same as above but for a fixed duration of 24 months
1998 (FD-MDT 12)	SLPB (single-lesion paucibacillary leprosy): 1 skin lesion PB: 2–5 skin lesions MB: ≥6 skin lesions	SLPB: Single supervised dose of rifampicin (600 mg), ofloxacin (400 mg), minocycline (100 mg) PB: Rifampicin 600 mg monthly plus dapsone 100 mg daily; 6 cycles in 9 months MB: Rifampicin 600 mg plus clofazimine 300 mg monthly and dapsone 100 mg plus clofazimine 50 mg daily; 12 cycles in 18 months
2003	PB: 1–5 skin lesions MB: ≥6 skin lesions	SLPB: Withdrawn PB and MB treatment regimen same as FD-MDT 12
2000 proposal	A (accompanied): MDT	Same for both PB and MB under supervision of close ones
2002 proposal	U (uniform): MDT	Uniform MDT of 6 months for both PB and MB cases

BI bacterial index, *MB* multibacillary, *PB* paucibacillary

The WHO FD-MDT Regimen [14]

PB: (1–5 skin lesions)—Rifampicin 600 mg monthly plus dapsone 100 mg daily; 6 cycles in 9 months.

MB: (≥6 skin lesions)—Rifampicin 600 mg plus clofazimine 300 mg monthly and dapsone 100 mg plus clofazimine 50 mg daily; 12 cycles in 18 months.

Image showing MDT blister packs for both paucibacillary (PB) and multibacillary (MB) leprosy in adults as well as childhood has been added in Fig. 6.1.

Fig. 6.1 **(a)** Adult MB-MDT pack. **(b)** Adult PB-MDT pack. **(c)** Child MB-MDT pack. **(d)** Child PB-MDT pack

Alternate Regimens (Non-WHO MDT)

With the advent of time, new regimens are being introduced as certain drawbacks are to be taken care of in the old multidrug therapy. A safe and effective alternative regimen is to be kept in store as emergence of drug resistance is inevitable in any large-scale treatment of a chronic infectious disease. Likewise, the transmission of disease has not been interrupted, and to break this chain of transmission, we need to cultivate new regimens. The current MDT regimen is still complicated as two types of drug administrations, i.e., monthly (supervised) and daily (self-administration), are involved. So if a patient fails to comply with self-administered daily treatment, he/she is virtually treated with rifampicin (RIF) monotherapy. Therefore, the current MB regimen is not RIF resistance-proof [15].

Thus a strong need to combat drug resistance and enhance the therapeutic efficacy has contributed to the introduction of monthly supervised regimens with new drug combinations coming into use.

Newer MDT Regimens

In recent times, certain drugs like fluoroquinolones and minocycline have been used to formulate new MDT regimens. They seem to be a good option in patients showing poor response, intolerance, or any contraindication to primary chemotherapy. Currently used newer drugs with their dose, mechanism of action, side effects, and contraindications have been enlisted in Table 6.2.

MB Cases

1. Fully supervisable, monthly administered regimens.
   - PMM combination: Rifapentine 900 mg, moxifloxacin 400 mg, and minocycline 100 mg (PMM) for 12 months [16].
   - ROM combination: Rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg for 12 months for MB cases.
2. 6-week quadruple regimen: Rifampicin 600 mg plus ofloxacin 400 mg plus clofazimine 100 mg plus minocycline 100 mg once a week for 6 weeks [17]
3. Once a month, supervised rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg in addition to self-administered dapsone 100 mg plus clofazimine 50 mg daily for 12 months [18].

PB Cases

- Single dose of ROM or RMM for all PB cases [19].
- 4-week, ofloxacin-containing regimen: Rifampicin 600 mg and ofloxacin 400 mg given in supervised doses daily for 4 weeks
- Once a month ROM for 6 months.

Table 6.2 Currently used newer drugs in leprosy

Name of the drug and dose	Mechanism of action	Adverse effects	Contraindications
1. Rifapentine (900 mg monthly)	Inhibits DNA-dependent RNA-polymerase of the bacteria interfering with bacterial cell replication	• Nausea • Vomiting • Headache • Discoloration of body secretions	Any previous history of allergy to the drug
2. Fluoroquinolones • Ofloxacin (400 mg monthly) • Moxifloxacin (400 mg monthly)	Inhibits α subunit of DNA gyrase, interfering with bacterial DNA replication	• Nausea • Diarrhea • Headache • Insomnia • Dizziness	Relative contraindication: Pregnant women and children
3. Minocycline (100 mg monthly)	Binds reversibly to the 30 S unit of the ribosome, blocking protein synthesis	• Nausea • Diarrhea • Headache • Dizziness • Mouth sores • Discoloration of the teeth in infants or young children	Pregnancy and patients <16 years of age
4. Macrolides • Clarithromycin (500 mg OD)	Inhibits bacterial protein synthesis by binding to the 50s ribosomal subunits of bacteria	• GI upset • Dizziness • Irritability • Hallucinations • Metallic taste in the mouth and confusion	Patients with prolonged QT interval and taking class Ia and class III anti-arrhythmic agents Relative contraindication: Pregnancy

DNA deoxyribonucleic acid, *RNA* ribonucleic acid

Accompanied MDT [20]

The entire supply of MDT drugs is provided to the patient at the time of diagnosis, and someone close to or important to the patient undertakes the responsibility of helping him or her complete a full course of treatment.

Uniform MDT [21]

A fixed duration of treatment of 6 months with rifampicin, dapsone, and clofazimine as for MB therapy is given for both PB and MB cases. Relapse rate is then assessed to see the response.

The advantages and disadvantages with the mentioned regimes are summarized in Table 6.3.

Table 6.3 Advantages and disadvantages of various regimens

Regimen	Advantages	Disadvantages
WHO MDT (in current form)	1. The issue of resistance to dapsone and other drugs already in use was addressed 2. Side effects due to long-term monotherapy were overcome 3. It promoted compliance of patient due to shorter duration of treatment, thus took care of the issue of default 4. It retained rifampicin in all therapeutic regimens owing to its strong bactericidal action and good efficacy even in monthly doses 5. It is cost-effective 6. Combination of drugs like dapsone and clofazimine in daily doses along with rifampicin in supervised monthly doses works well on persisters and reduces the chances of relapse	1. Continuation of treatment, till smear negativity in MB leprosy cases is difficult from operational point of view 2. The cure or endpoint of treatment of PB cases (smear-negative patients) has been more difficult to ascertain unlike in MB cases wherein the slit skin smears indicate disease activity
WHO FD-MDT regimen	1. Better patient compliance without significantly compromising the efficacy 2. Positive BI should not be the marker of continuation of treatment as it declines gradually during follow-up and may remain positive at the end of 12 or 24 months of therapy	1. Clinical activity may not correlate well with bacteriological activity and vice versa at the end of 12 months 2. High BI (>4) denotes poor cell-mediated immunity, so the chances of relapse due to presence of dormant bacilli (persisters) are more, warranting a longer duration of treatment 3. Bacteriological relapse occurred earlier than clinical worsening, demanding a long follow-up period with slit skin smear as a part of post-therapeutic surveillance 4. Post-therapy surveillance is not recommended, and patients are advised to report as soon as they notice any clinical signs of the disease activity
Other regimens: ROM, RMM_X, PMM_X, etc.	1. The use of new drug regimens will help to avoid the emergence of drug resistance as these involve either supervised or shorter duration of treatment	1. Costlier 2. Not easily available 3. Limited evidence

(continued)

Table 6.3 (continued)

Regimen	Advantages	Disadvantages
Accompanied MDT	1. It's an easier way to give supervised therapy 2. It involves the presence of family members in sharing the burden of disease 3. Contacts can be easily identified and treated likewise	1. Lacks evidence-based justification 2. Neglects the importance of regular contacts between healthcare workers with patients 3. Delays the identification of impairment and deformity
Uniform MDT	1. Uniform MDT merges leprosy with general healthcare services making it more operationally convenient 2. Increased compliance due to shorter duration makes it an acceptable regimen for MB patients 3. Addition of clofazimine to PB regimen helps in rapid regression of granulomas and further reduces the chances of relapse	1. Overtreatment of PB leprosy patients and undertreatment of MB patients, especially those with a high initial BI, are major drawbacks of this regimen 2. Relapse rate and chances of reaction are higher in MB cases due to short duration of treatment

R rifampicin, *O* ofloxacin, *M* minocycline, *P* rifapentine, *Mx* moxifloxacin

Resistance to MDT

Resistance to multidrug therapy (MDT) is one of the major obstacles in the treatment of Hansen's disease [22]. It can manifest in two forms:

1. Primary resistance: Presence of already resistant strains.
2. Secondary resistance: Development of resistance due to inadequate therapy or monotherapy.

In cases where resistance to a standard anti-leprosy drug is identified and documented, treatment regimens may be altered for the patient.

Rifampicin-resistant MB cases: A fully supervised regimen in two phases [15] is recommended.

- The intensive phase: Moxifloxacin 400 mg—clofazimine 50 mg—clarithromycin 500 mg—minocycline 100 mg all taken daily for 6 months.
- The continuation phase: Moxifloxacin 400 mg—clarithromycin 1000 mg—minocycline 200 mg all taken once monthly for 18 months.
- If available, ofloxacin may be replaced by moxifloxacin 400 mg, which has stronger bactericidal activity against *M. leprae* [23].

It has been observed that rifampicin-resistant patients are also expected to be resistant to dapsone [24].

Defaulter

A defaulter is a person who has not completed the scheduled 6 months of PB-MDT in 9 months and 12 months of MB-MDT in 18 months. It results in subtherapeutic dosing leading to drug resistance, disease progression, and continuation of transmission. A defaulter showing signs of new skin lesions or nerve involvement and any indication of lepra reaction should be immediately put on a new course of MDT according to the classification [25]. Busting myths and misconceptions associated with the disease and a well-equipped easily approachable healthcare facility help in timely completion of treatment minimizing the possibility of default.

Relapse

Relapse indicates the reappearance of clinical leprosy in the wake of successful completion of recommended anti-leprosy treatment. It is indicated by the appearance of new skin lesions and an increase in the bacteriological index by two or more units. Several risk factors associated with relapse are presence of persisters, reinfection, inadequate/irregular therapy, drug resistance, high initial BI, number and even size of skin lesions, and negative lepromin test [26].

Treatment should be started immediately as soon as a relapsed case is identified keeping in mind certain factors like type of leprosy, prior treatment taken, and drug resistance. In fact, antibiotic resistance tests should be done before initiating any therapeutic regime. Treatment of relapse is discussed in Table 6.4 [27].

Table 6.4 Recommended treatment regimens

	Resistance	Scenario	Treatment
1.	Relapse due to persisters	Relapse after a course of MB-MDT	Retreatment with WHO MDT depending on the type of disease (PB or MB-MDT)
2.	Relapse due to dapsone resistance	Relapse after previous cure with dapsone monotherapy	Standard WHO MDT
3.	Relapse due to rifampicin resistance or dapsone and rifampicin-resistant *M. lepra*	Primary or secondary dapsone-resistant MB cases who received standard WHO MB-MDT but did not take their clofazimine (situation equivalent to rifampicin monotherapy)	Clofazimine 50 mg daily for 24 months plus two of the following drugs for 6 months: Ofloxacin 400 mg daily/ minocycline 100 mg daily/ clarithromycin 500 mg daily, followed by: Ofloxacin 400 mg daily or minocycline 100 mg daily for the remaining 18 months

MB multibacillary, *PB* paucibacillary

Treatment of Lepra Reaction

Treatment of both type 1 (reversal reaction) and type 2 lepra reaction (erythema nodosum leprosum) is imperative, as they are accountable for permanent nerve damage, deformity, and disability associated with leprosy. Multidrug therapy is continued along with specific treatment for reactions which mainly depend on its severity.

For mild type 1 reactions characterized by inflammation in few of the existing skin lesions, nonsteroidal anti-inflammatory drug (NSAID) like aspirin 600 mg every 4–6 h with meals till sign and symptoms subside is sufficient. However, supportive care with rest and splinting the affected nerve carries great value in all lepra reactions. For severe reactions showing signs of markedly inflamed skin lesions with facial involvement, ulceration, neuritis, and impending or recent paralysis, prompt treatment with oral corticosteroids and NSAIDS is mandatory. Prednisolone started at a dose of 1 mg/kg/day is continued till clinical improvement is seen followed by gradual tapering by 10 mg every fortnightly and 5 mg every 15 days from 20 mg onwards.

Type 2 lepra reaction is characterized by crops of tender, evanescent, erythematous, subcutaneous nodules associated with fever and malaise. Mild type 2 reactions showing few ENL lesions can be managed with nonsteroidal anti-inflammatory drugs for a few weeks with slow tapering as clinical improvement is seen. For severe type 2 reactions, oral corticosteroids should be started at a dose of 1 mg/kg/day till clinical improvement is seen followed by tapering every week by 5–10 mg over 6–8 weeks. For severe recurrent ENL reactions and patients showing adverse reaction to prolonged corticosteroid therapy, drugs like clofazimine at a dose of 300 mg daily for 1 month with gradual tapering by 100 mg at an interval of 3 months and thalidomide 400 mg daily for 7 days with slow reduction by 100 mg on monthly basis can be added. Alternative drugs like cyclosporine, azathioprine, pentoxifylline, mycophenolate mofetil, and betamethasone pulse therapy have also been used with variable success.

Childhood Leprosy

As childhood leprosy is a marker for activity of the disease in the community, it has to be addressed in an equally serious tone as adult leprosy. The primary source of infection in this age group is household contacts.

In children <10 years of age, the doses should be preferentially calculated according to the weight of the child, i.e., dapsone 2 mg/kg/day, rifampicin 10 mg/kg, and clofazimine 1 mg/kg/day daily and 6 mg/kg monthly [28]. The drug schedule for childhood leprosy is outlined in Table 6.5 [28].

Table 6.5 MDT regimen for childhood leprosy

Age (years)	Paucibacillary (duration: 6 months)		Multibacillary (duration: 12 months)			
	Dapsone, daily dose, unsupervised (mg)	Rifampicin, monthly dose, supervised (mg)	Dapsone, daily dose, unsupervised (mg)	Rifampicin, monthly dose, supervised (mg)	Clofazimine unsupervised (mg)	Clofazimine, monthly dose, supervised (mg)
10–14	50	450	50	450	50 every other day	150
15 or above	100	600	100	600	50 daily	300

Leprosy and Pregnancy

- None of the anti-leprosy drugs are contraindicated in pregnancy.
- Rather, early initiation of MDT to prevent fetal damage and break the chain of transmission is the primary aim of management of leprosy in pregnancy, and hence treatment is started as soon as the diagnosis of leprosy is confirmed in a pregnant woman, irrespective of the trimester [29].
- Similarly the MDT is not contraindicated in lactation; however, regular follow-ups need to be maintained with the mother and child to look for any drug-related side effects and signs of reaction.
- For leprosy reactions during pregnancy and lactation, oral corticosteroids are the mainstay of therapy along with MDT. Other than steroids, clofazimine is the preferred choice as an anti-reaction drug [29].
- Drugs like thalidomide, methotrexate, cyclosporine, and azathioprine are contraindicated.

Leprosy and Tuberculosis

- Co-infection of leprosy and tuberculosis (TB) has been predominantly reported in borderline and lepromatous disease.
- Depressed cell-mediated immunity in leprosy by a defect in Toll-like receptor 2, poor response to chemokine ligand 2, and tumor necrosis factor alpha may either reactivate latent TB or make a person vulnerable to get new infection [30].
- Further steroid use in lepra reactions and treatment of silent neuropathy may be a triggering factor in this regard.
- The potential risk of development of rifampicin resistance secondary to monthly rifampicin in leprosy is of prime concern in treating patients co-infected with TB or where diagnosis is missed initially [31].

- Hence, proper screening of all leprosy patients is compulsory, especially if there are respiratory and constitutional symptoms with abnormal chest x-ray to rule out co-infection before starting chemotherapy.
- Management of TB with concomitant leprosy remains the same as according to WHO treatment categorization with addition of dapsone and clofazimine for leprosy.

Leprosy and Human Immunodeficiency Virus (HIV)

- Co-infection of leprosy with HIV has been predominantly reported in multibacillary leprosy.
- Standard multidrug therapy along with highly active antiretroviral therapy (HAART) is the treatment of choice in all cases of leprosy with concomitant HIV.
- Moreover, early institution of HAART enhances the treatment response leading to upward shift of all clinical forms of leprosy and faster withdrawal of steroids in lepra reactions.
- Increased incidence of type 1 lepra reaction and acute neuritis is commonly observed in seropositive patients with multibacillary leprosy which are usually managed with conventional treatment for reaction in addition to HAART.
- Antiretroviral therapy leads to restoration of immunity, unmasking underlying subclinical co-infections causing immune reconstitution inflammatory syndrome (IRIS) [32]. It presents clinically as type 1 reaction with the development of erythematous, edematous skin lesions which may develop unusual ulceration and neuritis with nerve paresis/paralysis.
- Patients with CD4 cell count under 50 cells/μL, with underlying opportunistic infection, or with high microbial burden are at stake for the development of IRIS [33].
- Such patients require careful monitoring of the dose of oral corticosteroids to ensure early detection and management of opportunistic infections. Anti-inflammatory drugs and specific antimicrobial agents may also be needed along with the continuation of HAART and MDT.

Non-acceptance to Clofazimine

- Intolerance to clofazimine is mainly seen due to its gastrointestinal side effects and discoloration and darkening of the skin.
- This discoloration is generally reversible when the drug is stopped, but some patients still refuse to accept it.
- The WHO advocates the use of ofloxacin 400 mg daily or minocycline 100 mg daily as substitutes for clofazimine in such cases. It also recommends monthly administration of ROM for 24 months as an alternative treatment [34].

Dapsone Toxicity

- Dapsone toxicity can present with a wide range of clinical presentations like exfoliative dermatitis, jaundice, and some severe adverse drug reactions like hemolytic anemia, dapsone hypersensitivity syndrome, agranulocytosis, and methemoglobinemia.
- The drug is stopped immediately in such scenario with no further modifications in MB cases. However, in PB leprosy, clofazimine may be substituted for dapsone for a period of 6 months [35].
- Use of second-line agents like ofloxacin and minocycline has also been reported [36].

Hepatosafe Regimen

- Out of the three conventional drugs of multidrug therapy, rifampicin and dapsone are hepatotoxic.
- Hence, a hepatosafe regimen has been recommended by WHO for patients intolerant to the above two drugs.
- The total duration of treatment in this regime is 24 months with the initial intensive phase consisting of daily clofazimine, ofloxacin, and minocycline or clarithromycin for a period of 6 months. The maintenance consists of daily clofazimine and ofloxacin or minocycline for 18 months [37]

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