

Review

Leprosy: An overview

Jyotsna A.Saonere

Department of Pharmacy, Government Polytechnic, Amravati, India. E-mail: saonereja@gmail.com.

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Leprosy is common in many countries worldwide, and in temperate, tropical, and subtropical climates. Approximately 100 cases per year are diagnosed in the United States. Leprosy is characterized by disfiguring skin sore, nerve damage, and progressive debilitation. Leprosy is caused by a bacterium which affects various parts of the body particularly the skin and nerves. Leprosy is difficult to transmit and has a long incubation period. Children are more susceptible than adults. Effective medications exist, and isolation of victims in "leper colonies" is unnecessary. The emergence of drug-resistant *Mycobacterium leprae*, as well as increased numbers of cases worldwide, has led to global concern about this disease. Early diagnosis reduces leprosy symptoms and complications. In this article, efforts have been taken to discuss pathophysiology symptoms and treatment of leprosy. The aim of this review is to make people aware of the complications of leprosy which can be prevented by taking preventive measures by educating the people about this disease and gives the idea about the herbal treatment of leprosy that would be beneficial for people.

Key words: Disfiguring, progressive debilitation, leper colonies.

INTRODUCTION

Leprosy or Hansen's disease (HD) is a chronic disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis* (Han et al., 2008). Named after physician Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign (Kenneth et al., 2004). Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes. Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of infection; infection results in tissue loss, so fingers and toes become shortened and deformed as the cartilage is absorbed into the body. Leprosy has affected

humanity for over 4,000 years, and was well-recognized in the civilizations of ancient China, Egypt, and India (Holden, 2009). In 1995, the World Health Organization (WHO) estimated that between 2 and 3 million people were permanently disabled because of leprosy at that time. In the past 20 years, 15 million people worldwide have been cured of leprosy (Walsch, 2007). Although the forced quarantine or segregation of patients is unnecessary in places where adequate treatments are available, many leper colonies still remain around the world in countries such as India (where there are still more than 1,000 leper colonies), China, Romania, Egypt, Nepal, Somalia, Liberia, Vietnam, and Japan. Leprosy was once believed to be highly contagious and was treated with mercury; all of which applied to syphilis which was first described in 1530. It is now thought that many early cases of leprosy could have been syphilis.

Abbreviations: **B group**, borderline group; **BI**, bacterial index; **CAM**, clarithromycin; **CLF**, clofazimine; **DDS dapsone**, Diaminodiphenylsulfone; **ENL**, erythema nodosum leprosum; **G6PD**, glucose 6 phosphate dehydrogenase; **I group**, indeterminate group; **LL type**, lepromatous type; **LVFX**, levofloxacin; **MINO**, minocycline; **M. leprae**, *Mycobacterium leprae*; **MB**, multibacillary; **MDT**, multidrug therapy; **OFLX**, ofloxacin; **PB**, paucibacillary; **RFP**, rifampicin; **SLL**, single lesion leprosy; **SPFX**, sparfloxacin; **TT type**, tuberculoid type; **WHO**, world health organization.

Causes

Leprosy is caused by the organism *M. leprae* (Kenneth J et al., 2004). It is not very contagious (difficult to transmit) and has a long incubation period (time before symptoms appear), which makes it difficult to determine where or when the disease was contracted. Children are more

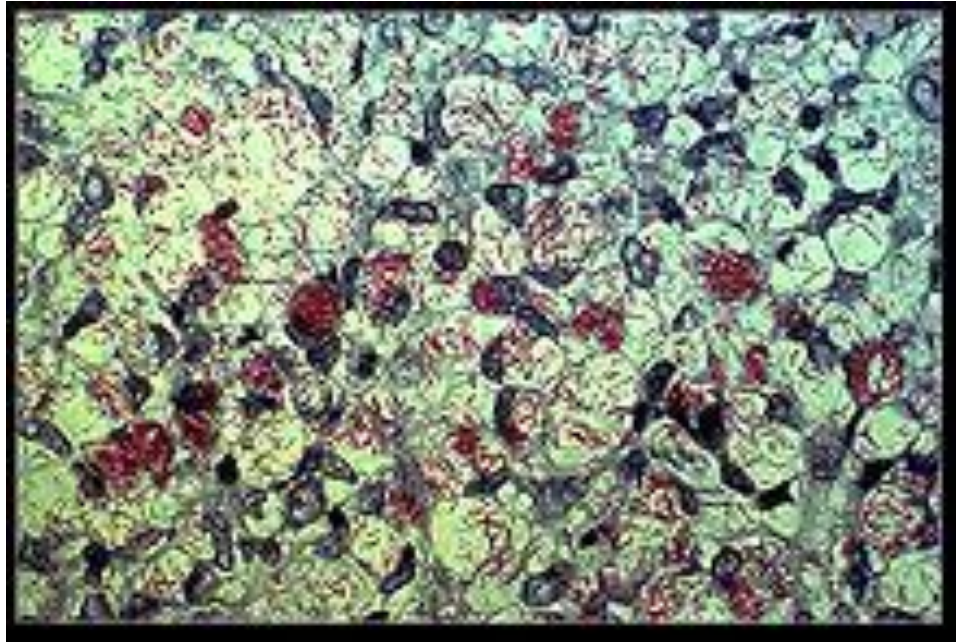


Figure 1. Causative agent of leprosy -*Mycobacterium leprae* (Kenneth et al., 2004).

susceptible than adults to contracting the disease.

M. leprae, one of the causative agents of leprosy is an acid-fast bacteria, *M. leprae* appear red when a Ziehl-Neelsen stain is used. *M. leprae* and *M. lepromatosis* are the causative agents of leprosy. *M. lepromatosis* is a relatively newly identified mycobacterium which was isolated from a fatal case of diffuse lepromatous leprosy in 2008. An intracellular, acid-fast bacterium, *M. leprae* is aerobic and rod-shaped, and is surrounded by the waxy cell membrane coating characteristic of *Mycobacterium* species (MCMurray, 1996) (Figure 1). Leprosy is caused/contracted by the following:

1. Person to person-leprosy spread from person to person through infected respiratory droplets;
2. Parents of someone with leprosy;
3. Children of someone with leprosy;
4. Brothers or sisters of someone with leprosy;
5. The extent of exposure;
6. Genetics;
7. Environmental conditions.

Types of leprosy

Indeterminate leprosy: A few hypopigmented macules; can heal spontaneously, persists or advances to other forms.

Tuberculoid leprosy: A few hypopigmented macules, some are large and some become anesthetic (lose pain, tactile and thermic sensation); some neural involvement in which nerves become enlarged; spontaneous resolution

in a few years, persists or advances to other forms.

Borderline tuberculoid leprosy: Lesions like tuberculoid leprosy but smaller and more numerous with less nerve enlargement; this form may persist, revert to tuberculoid leprosy, or advance to other forms.

Mid-borderline leprosy: Many reddish plaques that are asymmetrically distributed, moderately anesthetic, with regional adenopathy (swollen lymph nodes); the form may persist, regress to another form, or progress.

Borderline lepromatous leprosy: Many skin lesions with macules (flat lesions) papules (raised bumps), plaques, and nodules, sometimes with or without anesthesia; the form may persist, regress or progress to lepromatous leprosy.

Lepromatous leprosy: Early lesions are pale macules (flat areas) that are diffuse and symmetric; later many *M. leprae* organisms can be found in them. Alopecia (hair loss) occurs; often patients have no eyebrows or eyelashes. As the disease progresses, nerve involvement leads to anesthetic areas and limb weakness; progression leads to aseptic necrosis (tissue death from lack of blood to area), lepromas (skin nodules), and disfigurement of many areas including the face. The lepromatous form does not regress to the other less severe forms. Histoid leprosy is a clinical variant of lepromatous leprosy that presents with clusters of histiocytes (a type of cell involved in the inflammatory response) and a grenz zone (an area of collagen

separating the lesion from normal tissue) seen in microscopic tissue sections.

Symptoms

Leprosy symptoms generally appear three to five years after a person becomes infected with bacteria that cause the disease. The symptoms include:

1. Skin lesions that are lighter than your normal skin color; lesions have decreased sensation to touch, heat, or pain and lesions do not heal after several weeks to months;
2. Numbness or absent sensation in the hands, arms, feet, and legs;
3. Muscle weakness;
4. Eye problems;
5. Skin rash;
6. Skin stiffness;

EXAMS AND TESTS

Different tests can be employed in the diagnosis of different type of leprosy. The different test includes:

1. Lepromin skin test can be used to distinguish lepromatous from tuberculoid leprosy, but is not used for diagnosis.
2. Skin lesion biopsy.
3. Skin scraping examination for acid fast bacteria.

Prevention of leprosy

An early diagnosis will reduce leprosy symptoms and complications. Prevention consists of the following:

1. People who are in immediate contact with the leprosy patient should be tested for leprosy;
2. Annual examinations should also be conducted on these people for a period of five years following their last contact with an infectious patient;
3. Reconstructive surgery is aimed at preventing and correcting deformities;
4. Comprehensive care involves teaching patients to maintain a range of movement in finger joints and prevent the deformities from worsening;
5. BCG offers a variable amount of protection against leprosy as well as against tuberculosis (Fine, 1996);
6. Efforts to overcome persistent obstacles to the elimination of the disease include improving detection, educating patients and the population about its cause, and fighting social taboos about a disease that has caused its patients historically to be considered "unclean" or "cursed by God" as outcasts. Leprosy is not a hereditary

disease. Where taboos are strong, patients may be forced to hide their condition (and avoid seeking treatment) to avoid discrimination. The lack of awareness about Hansen's disease can lead people to believe (falsely) that the disease is highly contagious and incurable.

Genetics

Several genes have been associated with a susceptibility to leprosy (Table 1). Recent research suggests that there is a defect in cell-mediated immunity that causes susceptibility to the disease. Less than ten percent of the world's population is actually capable of acquiring the disease. The region of DNA responsible for this variability is also involved in Parkinson disease, giving rise to current speculation that the two disorders may be linked in some way at the biochemical level. In early 2003, an international team of scientists conducted a genome scan in Vietnamese multiplex leprosy families and found that susceptibility to leprosy was significantly linked to region q25 on the long arm of chromosome 6. Further confirmation of the chromosome 6 locus was provided by high-resolution linkage mapping in simplex leprosy families. Now, in a continuation of these findings, the team has pinpointed the chromosome 6 susceptibility locus to the 5' regulatory promoter region shared by both the Parkinson's disease gene *PARK2* and its co-regulated gene *PACRG* (Buschman et al., 2004). According to The leprosy Mission Canada, most people (about 95% of the population) are naturally immune to the disease.

Risk factors

At highest risk are those living in endemic areas with poor conditions such as inadequate bedding, contaminated water and insufficient diet, or other diseases that compromise immune function. However, studies show that, oddly enough, HIV does not increase risk of leprosy infection. Presumably this is because of differences between the modes of immunity involved.

Treatment

Treatment principles for leprosy

The major goals of the leprosy control program are (1) early detection of patients; (2) appropriate treatment; and (3) adequate care for the prevention of disabilities and rehabilitation. Because leprosy is an infectious disease, antibiotic therapy plays a pivotal role in the management of newly diagnosed patients.

There are several effective chemotherapeutic agents

Table 1. Type of gene responsible for susceptibility of leprosy.

Name	Locus	OMIM	Gene
LPRS1	10p13	609888	
LPRS2	6q25	607572	PARK2, PACRG
LPRS3	4q32	246300	TLR2
LPRS4	6p21.3	610988	LTA
LPRS5	4p14	613223	TLR1
LPRS6	13q14.11	613407	

against *M. leprae*. Dapsone (diaphenylsulfone, DDS), rifampicin (RFP), clofazimine (CLF, B663), ofloxacin (OFLX), and minocycline (MINO) constitute the backbone of the multidrug therapy (MDT) regimen recommended by WHO. Other chemotherapeutic agents, like Levofloxacin (LVFX), sparfloxacin (SPFX), and clarithromycin (CAM) are also effective against *M. leprae* (Sugita et al., 1996). WHO has designed very practical kits containing medication for 28 days, dispensed in blister packs, for both PB and MB leprosy (Ishii et al., 1997). The blister pack medication kit for SLPB leprosy contains the exact dose for the one-time administration of the three components of the MDT regimen.

Following the classification according to the flowchart PB patients receive 600 mg RFP monthly, supervised, and 100 mg dapsone daily, unsupervised, for 6 months. SLPB patients can be treated with a single therapeutic dose consisting of 600 mg RFP, 400 mg OFLX, and 100 mg MINO. MB cases are treated with 600 mg RFP and 300 mg CLF monthly, supervised and 100 mg dapsone and 50 mg CLF daily, for 12 months. Reduced doses of this regimen are appropriately determined for children (WHO, 1998, 1988, 1982).

Directly, monthly supervised treatment of RFP is very important to avoid drug resistance. An additional 27 days of treatment with dapsone (and CLF) are mandatory and, health workers should ensure that regular and daily, uninterrupted drug intake is performed.

Multidrug therapy (MDT)

MDT is a key element of the leprosy treatment and elimination strategy. For both PB and MB leprosy, RFP is central to the antileprosy drug regimen (Table 2a,b, and c). It has been proven that monotherapy in leprosy will result in the development of resistance to the drug used. Thus, monotherapy with dapsone or any other antileprosy drug should be considered unethical practice. Tables 3 and 4, respectively, show the pharmacological effects of each drug and the recommended laboratory monitoring.

The drug rifampicin (RFP) is administered in a single monthly dose, a protocol for which no significant toxic effect has been reported. Exceptionally bactericidal against *M. leprae*, a single dose of 600 mg of RFP is

capable of killing 99.9% or more of viable organisms. However, the rate of killing is not proportionately enhanced by subsequent doses. It has been suggested that RFP may exert a delayed antibiotic effect for several days, during which the organism's multiplication is inhibited. The high bactericidal activity of RFP made feasible the application of the single monthly dose, which is cost-effective for leprosy-control programs. At the start of the treatment, the patient should be informed of the usual side effect of a slight reddish coloration of urine.

Diaminodiphenylsulfone (DDS, dapsone), which is bacteriostatic or weakly bactericidal against *M. leprae* was for years the mainstay in the treatment regimen for leprosy (Peter et al., 1975) until widespread resistant strains to the drug were reported. Subsequently, its use in combination with other drugs has become essential to slow or prevent the development of resistance (Ahmad et al., 1980). The drug has demonstrated an acceptable level of safety in the dosage used in MDT. Besides occasional cutaneous eruptions, side effects that necessitate discontinuation are rare. Patients known to be allergic to any of the sulpha drugs should be spared dapsone. Anemia, hemolysis, and methemoglobinemia may develop but are more significant in patients deficient for glucose-6-phosphodihydrogenase (G6PD).

Clofazimine (CLF), which preferentially binds to mycobacterial DNA, both inhibits mycobacterial growth and exerts a slow bactericidal effect on *M. leprae* (Schaad-Lanyi et al., 1987; Morrison et al., 1976). Anti-inflammatory properties have been suggested, for the drug controls erythema nodosum leprosum reactions by mechanisms still poorly understood. Most active when administered daily, the dosage used for MDT is well tolerated and has not shown significant toxicity. Because CLF is a repository drug, stored in the body after administration and slowly excreted, it is given as a loading dose of 300 mg once a month to ensure that the optimal amount of CLF is maintained in the body tissue, even if patients occasionally miss their daily dose. Patients starting the MDT regimen for MB leprosy should be informed of side effects including brownish black discoloration and dryness of skin. These usually disappear within a few months of treatment suspension.

Recently three more drugs have shown bactericidal activity against *M. leprae*. These are ofloxacin (OFLX) -a

Table 2A. Multidrug therapy for multibacillary (MB) leprosy.

Variable	PFP* (mg/d)	Dapsone (mg/d)	CLF
Adult 50-70 kg	600	100	50 mg/d and 300 mg/m*
Child 10-14 years	450	50	50 mg/d and 150 mg/m*
Less than 10	300	25	50 mg twice/w and 100 mg/m*

*PFP and CLF monthly doses are given under supervision.

Table 2B. Multidrug therapy for paucibacillary (PB) leprosy.

Variable	PFP* (mg/m)	Dapsone (mg/d)
Adult 50-70 kg	600	100
Child 10-14 years	450	50
Less than 10	300	25

*PFP and CLF monthly doses are given under supervision.

Table 2C. Multidrug therapy for single lesion paucibacillary (SLPB) leprosy.

Variable	PFP(mg)	OFLX(mg)	MNO(mg)
Adult 50-70kg	600	400	100
Child 5-14 years	300	200	50

Not recommended for pregnant women and children less than 5 years old.

Table 3. Pharmacological effect of drugs applied for leprosy.

RFP	Bactericidal
Dapsone	Bacteriostatic, weakly bactericidal
CLF	Slow bactericidal
OFLX	Bactericidal
MINO	Bacteriostatic
SPFX	Bactericidal
CAM	Bacteriostatic, weakly bactericidal

fluoroquinolone, minocycline (MINO) -a tetracycline, and clarithromycin-a macrolide. Ofloxacin (OFLX) is a synthetic fluoroquinolone that acts as a specific inhibitor of bacterial DNA gyrase and has shown efficiency in the treatment of *M. leprae* (Nakashima et al., 1992). Chromosome resistance of negligible clinical relevance has been reported.

Minocycline (Minocycline (MINO) is a semisynthetic tetracycline (Fajardo et al., 1995). It achieves selective concentration in susceptible organisms and induces bacteriostasis by inhibiting protein synthesis.

However, from the curative and cost-effectiveness points of view, the WHO-recommended, time-honored MDT remains to date the best combination regimen of the worldwide leprosy-control programs.

Treatment of PB leprosy

In PB patients, it is assumed that 6 months of treatment with RFP alone can ensure a complete clearing of the bacteria. However, to prevent RFP resistance dapsone has been added. The attainment of clinical inactivity should not be the condition guiding the continuation of MDT in PB patients, because these patients are virtually always cleared of viable bacteria in 6 months with the WHO-MDT regimen. Hence, one should keep in mind that clinical activity in PB leprosy does not necessarily directly correlate with bacterial multiplication. In a substantial proportion of patients, clinical inactivity may not be achieved in 6 months even after a complete clearing of the organisms. Follow-up studies of PB

Table 4. Laboratory monitoring for drugs used to treat leprosy.

Drug	Laboratory studies	frequency
Initial studies for all drugs	CBC, platelets, UA, Chemistry	Baseline
DDS	G6PD, CBC	Every 6 months
RFP	CBC, platelets, Chemistry	Every 3 months
CLF	No recommended lab. studies	
Thalidomide	CBC	Every 2 months

patients in MDT's field trials have shown that complete clearing of lesions takes 1-2 years after treatment discontinuation. The incidence of relapses in PB patients is very low, and, to date, the correlation between disease activity status at the time of treatment completion and subsequent relapse is not well documented. Nevertheless, the accuracy of the initial classification of patients in the PB category is a determining factor of long-term results.

Treatment of SLPB

In 1997, WHO initiated the supply of special ROM(R: rifampicin. O: Ofloxacin. M: minocycline) blister packs to India, Bangladesh, Nepal, and Brazil for the treatment of SLPB leprosy. The 7th WHO expert committee on leprosy recommended the use of a combination of RFP 600 mg, OFLX 400 mg and MINO 100 mg (ROM) for the treatment of two categories of leprosy patients. Patients presenting with SLPB leprosy could be treated with a single dose of ROM. Both experimental and clinical studies have shown the bactericidal effectiveness of these drugs, either alone or in combination. Therefore, for the treatment of SLPB leprosy, WHO advocates a flexible attitude to the decision of whether to use a single dose ROM or the standard WHO-MDT for 6 months.

Treatment of MB leprosy

RFP remains the major component of the MDT regimens, clearing most RFP-susceptible strains of *M. leprae* with a few monthly doses. Recently it has been shown that the daily combination of dapsone and CLF is highly bactericidal. The combination has been very effective on RFP-resistant mutants in an untreated MB leprosy patient within 3 to 6 months. For the treatment of MB leprosy, controlled and reliable clinical trials have demonstrated that MDT is generally effective within 24 months or less. Such observations led WHO to recommend 12 months as an acceptable duration for the MDT regimen in the efficient treatment of MB leprosy.

Some concerns arose regarding this 12-month regimen for the treatment of high bacteriological index patients. Observations have shown that a high bacteriological

index in MB patients correlates with a high risk for the development of adverse reactions and nerve damage during the second year of treatment. Also, a high bacteriological index at the start of the treatment regimen has been correlated not only with a slow disappearance of skin lesions but also with a high index at the end of the 12-month regimen compared with patients starting with a lower bacteriological index. However, it was found that most of the high bacteriological index patients will continue to improve after the completion of the 12-month regimen. Nevertheless, an additional 12 months of MDT for MB leprosy is needed for patients showing evidence of deterioration.

Provided there is a strict adherence to the regimen by the patient, the shortening of the MDT for MB leprosy from 24 to 12 months will not lead to a higher risk for the development of resistance to RFP. Several studies have demonstrated that a few doses of RFP are able to clear all the organisms susceptible to RFP. The naturally occurring RFP-resistant mutants are very sensitive to the CLF-dapsone combination, leaving very little chance for any bacteria to survive 12 doses of MDT.

The prevalence of MB patients with a high bacterial index is decreasing in most programs. WHO has estimated their proportion among newly detected cases to less than 15%. There is evidence that 3 to 6 months of administration of MDT clears all live organisms. Also, for reasons of nonavailability or nonreliability of skin smear services, increasing numbers of leprosy control programs are classifying leprosy patients on clinical criteria alone. A factor of supreme importance in the surveillance of the treatment is the determination by the control program of patients with high bacteriological index and those with high risk of developing reaction and neuritis. This surveillance should be done by both clinical and bacteriological methods. Such selected patients may be kept on surveillance for 1 to 2 years in order to detect deterioration and adverse reactions as early as possible. Signs of deterioration are an indication of the necessity of an additional course of 12 months of MDT. In general, reactions are successfully managed by a standard course of prednisolone. A key element of the surveillance is the education of patients at the end of the treatment program. The benefit of the treatment program would be seriously undermined if the patients were to ignore the symptoms and signs of relapses, and not report them at their

slightest manifestation. MB leprosy patients who do not accept CLF can be treated with the monthly administration of 24 doses of ROM.

MDT and *M. leprae*

Persisting *M. leprae* are defined as viable organisms which are fully susceptible to the drugs but survive despite adequate treatment with antileprosy drugs, probably because they are in a low or dormant metabolic state. To the best of our knowledge, drugs that can clear these persisting organisms are as yet undetermined, although RFP is known for its capability to kill persisting organisms in another mycobacterial disease, tuberculosis. Evidence so far accumulated has shown that persisting organisms, even though present, do not play a key role in the occurrence of relapses in leprosy among patients treated with MDT.

In most patients, the presence of dead bacilli in the skin and other tissues seems to be pathogenically insignificant and the dead organisms are gradually cleared away by the body's phagocytic system. The results of several large-scale, long-term field trials show that the rate of clearance of dead bacilli is about 0.6 to 1.0 logs per year and is not enhanced by MDT. However, in a very small proportion of patients, antigens from dead bacilli can provoke immunological reactions, such as the (late) reversal reaction, causing serious nerve damage and subsequent disabilities. Patients should be aware of this potential advent. These reactions are effectively managed by corticosteroids such as prednisolone.

Although the risk of possible endogenous reactivation is negligible when adequate chemotherapy has been completed, evidence exist for other mycobacterioses, like tuberculosis, that immunosuppressive drugs, like prednisolone, can accelerate the multiplication of organisms in a dormant state and cause a disseminated reactivation. Nothing of the like has been documented in leprosy. In case steroid therapy expected to exceed 4 months, prophylactic measures should be considered. Daily administration of 50 mg of CLF has been used in these cases and should be continued throughout the course of steroid therapy. However, these patients should not be re-entered into the case registry.

MDT AND DRUG-RESISTANCE

Resistance of *M. Leprae* to existing major anti-leprosy drugs has been worldwide reported. It has become imperative to develop paradises to overcome this problem, the magnitude of which was selective. Actually resistance to dapsone was the most reported. Subsequently regimens of the MDT were designed on the principle that they would be effective against all the strains of *M. leprae* regardless of their susceptibility to dapsone.

Reports on RFP-resistant leprosy came second to those of dapsone in term of frequency. Currently, the problem of RFP-resistant leprosy is trivial; however, selective non-compliance with dapsone and/or CLF by patients may facilitate the selection of RFP-resistant strains. This resistance to RFP is believed to develop as a result of its use in monotherapy or in combination with dapsone, to dapsone-resistant patients.

It has been estimated that an advanced, untreated MB patient harbors about 11 logs live organisms. Out of these, the proportion of naturally-occurring drug-resistant mutants is estimated to be 1 in 7 logs for RFP; 1 in 6 logs each for dapsone and CLF. The organisms resistant to one drug will be susceptible to the other drugs in MDT as their mechanisms of action are different. To date, reports of relapses after treatment with MDT have been rare. Their management with the same regimen has been equally effective.

All experimental and clinical facts indicate that there is no antagonism among the drugs comprising MDT. The experience with MDT so far has shown the combination to be the most effective one. Recently, genetic profiles of drug-resistant strains have been elucidated (Table 5).

Leprosy reaction and its treatment

Leprosy affects all aspects of patients' life (Reviewed in (Jacobson et al., 1999). Its reactions, known under the label "Leprosy reactions" include among their worst consequences, irreversible nerve damage and disabilities. Fortunately, these reactions have become gradually well documented and, if timely detected, they are eventually preventable. They occur in all PB and MB (B group and LL type) patients, most commonly during chemotherapy. PB and MB (B group) cases develop type 1 reaction (reverse reaction: RR), and type 2 reaction (erythema nodosum leprosum: ENL) occurs in MB (LL type) patients. Some data seem to indicate a trend toward a reduction in the frequency and severity of ENL in MB leprosy patients on MDT. These data may be attributable to the anti-inflammatory effect of CLF (Helmy et al., 1971). On the other hand, a temporary increase in the reporting of reversal reactions (type 1) has been noted in MB leprosy patients in their first year of MDT. The exact meaning of this observation remains unclear. One of the most likely explanations is the improvement of early and specific detection capability. Usually these reactions respond satisfactorily to prednisolone (Rook et al., 1999) along with thalidomide or CLF (Table 6) (Jacobson et al., 1999). In the case of permanent impairment, methods for rehabilitation must be addressed.

Relapse of leprosy

Evaluating the effectiveness of a chemotherapeutic regimen is essential to the leprosy-control program. One

Table 5. *Mycobacterium leprae*-resistant gene.

Drug	Gene	Function of gene
RFP	rpoB	DNA dependent-RNA polymerase β subunit
DDS	folP	dihydropteroate synthesis
CLF	?	?
OFLX	gyrA	DNA gyrase

Table 6. Treatment of lepra reaction.

Reaction	Prednisolone	CLF	Thalidomide
Reversal reaction (type 1)	up to 1 mg/kg/d then gradually reduced		
ENL (type 2)	up to 1 mg/kg/d then gradually reduced	up to 300 mg	up to 400 mg

Maximum daily dose is shown when single use combination therapy is recommended in ENL. Thalidomide should be avoided in women of childbearing age.

of the best methods of evaluation is the monitoring of relapse after the completion of a respected treatment protocol (Dasananjali et al., 1984). Data gathered by the Action Programme for the Elimination of Leprosy, WHO, from a number of control programs show that the relapse rate is very low (0.1% per year for PB and 0.06% per year for MB on the average). The program seems to be accepted worldwide. A likely explanation of this trend is probably the low frequency of side effects.

For MB patients, WHO has set 12 months or more of MDT as acceptable criteria for a sustainable cure and removal from registries, special mention has been granted to education. In this regard, a first emphasis has been put on the vital necessity for patients to know the signs and symptoms of reactions and relapses. Equally important is the obligation for an immediate reporting of the earliest manifestation of these signs to the relevant health centers. Improvements in the control program are such that it is no longer necessary to continue active surveillance after MDT programs. What remains mandatory as mentioned before is the reporting of any new lesions to the program even after a single dose of MDT.

Prolonged treatment

Overzealous or emotional attitudes should be avoided. Hence, reasons such as compliance with concerned patients' wishes or possible doubt about the effectiveness of the regimen as designed by WHO may bring some to feel the need to continue with dapsone monotherapy after a regular course of MDT. Such an attitude should be discouraged. Some reports have suggested a strong correlation between several years of dapsone monotherapy and a high frequency of relapse, especially in MB leprosy patients. For this reason, WHO's MDT for 12 months is highly recommended. There is no doubt that

pertinent aspects of the pathophysiology of leprosy are not yet completely understood, but attitudes and guidelines codified for the management of this disease are generally the result of carefully controlled studies by a devoted community of competent clinicians, scientists and leprosy workers. A strong recommendation is then to respect these now worldwide-accepted guidelines.

Side effects of drugs

One of the risks of combination therapy is probably the collective side effects. Fortunately, side effects reported worldwide after the use of MDT in thousands of patients remain mild and rare. However, the attribution of the adverse reactions to the individual constituents of the MDT should be clearly and unequivocally established. Such an attitude will lay the way for the use of new antileprosy drugs. Among the troublesome side effects is the common brown-black skin discoloration induced by CLF. Its appearance starts around the third month. An observable decrease is noticed beginning around 6 months after stopping the regimen and usually by 12 months the skin has returned to its normal pigmentation. In dry climatic settings, trivial annoyances like xerosis may accompany such discoloration. Xerosis can be easily managed by the use of moisturizers. Reducing exposure to sunlight is also advised.

Dapsone occasionally causes severe systemic, cutaneous, or hematological hypersensitivity or toxic effects. In some PB patients it has been successfully substituted with CLF in a dosage similar to that used for MB patients for 6 months. When dapsone must be stopped, treatment may be continued in MB patients with RFP and CLF in the standard dosage.

RFP may be replaced by a daily regimen of 400 mg of OFLX and 100 mg of MINO in association with the daily administration of 50 mg of CLF for the first semester. This

Table 7. Comparison of genome features.

Feature	<i>M. leprae</i>	<i>M. tuberculosis</i>
Genome size (bp)	3,268,203	4,411,532
G+C (%)	57.79	65.61
Protein coding (%)	49.5	90.8
Protein-coding genes (no.)	1,604	3,959
Pseudogenes (no.)	1,116	6
Gene density (bp per gene)	2,037	1,114
Average gene length (bp)	1,011	1,012
Average unknown gene length (bp)	338	653

(Nature 409:1007-11, 2001)

regimen is to be followed by daily administration of 50 mg of CLF, 400 mg of OFLX or 100 mg of MINO for the next 18 months. This regimen requires direct supervision in a referral center.

MDT and medication irregularity

Irregularity in administration of medication can cause serious harm to the MDT program. Not only may the patient become a source of contamination, but also the consequences may range from delayed and incomplete cure to the progression of the disease's activity and the development of disabilities and deformities. Concerns about the development of multidrug resistance must be taken seriously. It should be a matter of serious concern if a PB patient after 9 months has not completed the 6-month course of MDT. Equally dangerous would be a situation in which an MB patient after 18 months had not completed 12 months of the MDT course. Whenever possible, efforts should not be spared to bring back patients with lax discipline for adequate assessment and treatment. Such a defaulter, on returning to the health center for treatment, should be given a new course of MDT if he shows one or more of the following signs: (1) reddish or elevated skin lesions; (2) new skin lesions since last examination; (3) new nerve involvement since last examination; (4) lepromatous nodules; and (5) signs of ENL or reversal reaction.

MDT and HIV, Pregnancy, and TB

Existing data has shown that the response to MDT by leprosy patients infected with HIV has been similar to that of all other leprosy patients (Milanga et al., 1999). Hence, HIV infection in leprosy patients is not a contraindication for MDT. Leprosy management remains the same as in non-HIV-infected leprosy patients.

It is established that pregnancy exacerbates leprosy. Fortunately, MDT during pregnancy appears to be safe; no contraindications have been established currently

(Lockwood et al., 1999). CLF is excreted through breast milk and can cause mild discoloration of the infant.

MDT is not contraindicated in patients suffering from tuberculosis. However, because WHO's MDT for leprosy is not the ideal treatment for tuberculosis, an appropriate antitubercular regimen should be added to the antileprosy MDT in patients in whom the two diagnoses are confirmed. If daily RFP is part of the antituberculosis treatment, there is no need to administer monthly RFP as part of the leprosy MDT.

Failure of the MDT: lack of clinical and bacteriological improvement

A total lack of clinical and bacteriological clearing can occur in a small number of patients under MDT. Poor drug compliance and debilitating, recurrent infections seem the most likely explanation for such unresponsiveness. Poor compliance with medicine administration would generally be solved by supervised drug administration and health education, but recurrent infection needs thorough investigation (including, when indicated, tests for HIV infection) and appropriate management.

Vaccination

Vaccination against the leprosy bacillus may be considered. BCG vaccination is reported to be partially effective for protection against leprosy (Bertolli et al., 1997). However, a worldwide BCG vaccination program against *M. leprae* is not economically feasible; a cost-effective DNA vaccine could become a promising substitute (Rook et al., 1999). Currently, vaccination against leprosy is not available, leaving MDT the only adequate weapon against *M. leprae* in the global leprosy-control program. The recent, considerable progress in molecular engineering has allowed the elucidation of the entire sequence of the *M. leprae* genome (Table 7 and 8) (Cole et al., 2001). New vaccine strategies will probably develop, using these genomic sequence techniques.

Table 8. Herbal treatment for leprosy.

Name of plant	Botanical name	Part of plant used	Indication
Neem	<i>Azadirachta indica</i> Family- Meliaceae	Seeds, leaves, bark, flower, fruit, root, kernel	Leprosy, antiinflammatory, antibacterial, antimalaria, Diabetes mellitus, in blood pressure, antarrhythmic, antipyretic, antifungal, sporicidal, diuretic, ulcer, gastrointestinal problem.
Chaulmoogra oil	<i>Hydnocarpus anthelminthica</i>	Fruits, seeds	Leprosy
Hydrocotile or Gotu Kola	<i>Centella Asiatica</i>	Rhizomes or whole plant	Leprosy, psoriasis, headaches, diuretic, fever, varicose veins, inflammation, rheumatism and wounds.
Psoralea or Babchi	Psoralea	Seeds	Leprosy and skin disease

CONCLUSION

Leprosy is a chronic endemic disease which is characterized by disfiguring skin sore, nerve damage, and progressive debilitation. Leprosy is caused by a bacterium which affects various parts of the body, including in particular the skin and peripheral nerves. The long and asymptomatic disease incubation period as well as its insidious symptoms can lead to difficulties in the diagnosis of early and advanced cases. The early diagnostic is crucial for prevention of deformities and disabilities and also very important for a better quality of life for patients with leprosy. Educating the people regarding this disease and its symptoms and complications can reduce the risk of this disease to spread in future; by taking preventive measures educating the people regarding symptoms and treatment of leprosy.

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