

# Relapse in leprosy

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## ABSTRACT

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Leprosy is unique in terms of the nature of the causative organism (*Mycobacterium leprae*), the chronicity of the disease, its prolonged treatment and the definitions of “cure” and “relapse.” The principal mode of assessing the efficacy of therapeutic regimens in leprosy is the “relapse rate.” There are wide variations in estimates of relapse rates after the World Health Organization (WHO) multidrug therapy in different regions. The important predisposing factors for relapse include the presence of “persister” bacilli, monotherapy, inadequate/irregular therapy, presence of multiple skin lesions/thickened nerves and lepromin negativity. The conventional methods of confirming activity or relapse in an infectious disease (demonstration and/or culture of the etiologic agent) have limited utility in leprosy because of the difficulty in demonstrating bacilli in paucibacillary (PB) cases and absence of a method of *in vitro* cultivation of *M. leprae*. Bacteriological parameters are useful in multibacillary (MB) leprosy, whereas in PB leprosy, the criteria for relapse depend primarily on clinical features. Although there are no widely available serologic tests for leprosy other than in a research setting, various immunological tests may be useful for monitoring patients on chemotherapy as well as for confirming suspected cases of relapse. The main differential diagnoses for relapse are reversal reactions, erythema nodosum leprosum and reactivation/resistance/reinfection. The most reliable criteria for making an accurate diagnosis of relapse include clinical, bacteriological and therapeutic criteria. Additional ones that may be used, depending on the setting, are histopathological and serologic criteria. Relapsed cases of leprosy should be identified and put back on chemotherapy as soon as possible to prevent further disability and transmission of infection. Factors that should be considered in choosing an appropriate regimen are the type of leprosy (PB or MB), previous treatment and drug resistance. Occasionally, clinicians may need to use their judgement to modify the standard WHO treatment regimens according to the scenario in each patient.

**Key words:** Leprosy, reactivation, reinfection, relapse, resistance

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## INTRODUCTION

Relapse of diseases, acute or chronic, caused by bacterial infections is quite common. Usually, relapse indicates a failure to treat the infection thoroughly, which is compounded by irregular treatment, particularly in chronic disease.

The treatment of leprosy, compared with other infectious diseases, is unique in terms of the fixed dose and duration of regimens and also in terms of the definition of “cure.” Often, termination of treatment is based on completion of the recommended duration of treatment rather than disappearance of clinical signs and symptoms, which led to initiation of treatment in the first place.

Thus, the principal mode of assessing the efficacy of the therapeutic regimens in leprosy is the “relapse rate.” A very low relapse rate over an adequate period of observation indicates that the regimen used has been effective and this is why prolonged periods of surveillance are recommended by the World Health Organization (WHO) for all patients who have been declared “cured” after receiving multidrug regimens.

## DEFINITION

The definition of “relapse” can be understood only in the context of the definition of “cure.” In the era of Dapsone monotherapy, a patient with multibacillary (MB) disease was declared “disease arrested” when skin lesions resolved and when 3 monthly consecutive

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skin smears were negative for acid-fast bacilli (AFB), after which antileprosy treatment was continued for another 5–10 years or even a life time. A paucibacillary (PB) patient was declared “disease free” when all skin lesions resolved, with no infiltration and no erythema and the nerves were no longer painful or tender, after which antileprosy treatment was continued for 3–5 years.<sup>[1]</sup> With the advent of multidrug therapy (MDT), such rigid clinical criteria for cure have lost their importance. A leprosy patient is defined by the WHO as one who is found to have signs and symptoms of the disease and who requires chemotherapy. As of 1995, WHO recommends 1 year of MDT for MB patients (12 pulses in 18 months) and 6 months (six pulses in 9 months) for PB patients. At any point in time during therapy, the patient should have ingested two-third of the pulses till that time. For operational purposes, once a patient receives adequate chemotherapy, he is considered “cured.” Histopathological resolution of the lesions and clinical subsidence of the disease take place months to years after antileprosy treatment is stopped.

Several definitions have been proposed for relapse in leprosy.<sup>[1]</sup>

1. Guide to Leprosy Control (WHO 1988):  
“A patient who successfully completes an adequate course of MDT, but who subsequently develops new signs and symptoms of the disease either during the surveillance period (2 years for PB and 5 years for MB leprosy) or thereafter.”
2. Becx-Bleumink lists several criteria for relapse,<sup>[2]</sup> which include:
  - a) new skin lesions
  - b) new activity in previously existing skin lesions
  - c) bacteriological index (BI) 2+ or more in two sets of skin smears
  - d) new nerve function loss
  - e) histological evidence of relapse in skin or nerve biopsy
  - f) lepromatous activity in the eye(s)
3. Relapse in PB patients:
  - a) Beorrigter *et al*,<sup>[3]</sup> – “appearance of a new skin lesion or increase in size of pre-existing skin lesion, provided there is either strong clinical or definite histopathological evidence (or both) of leprosy in such a lesion.”
  - b) Pandian *et al*,<sup>[4]</sup> proposed seven criteria for defining relapse in PB – “extension of the lesion, infiltration, erythema, occurrence of fresh lesions, pain and tenderness of nerve,

new paralysis of muscles and bacteriological positivity.”

Regardless of the definition used for a case of relapse, it is important to remember that relapse in MB cases is relatively easy to recognize clinically while relapse in PB cases may be difficult to distinguish clinically from reversal reaction occurring some time after therapy is completed.

## RELAPSE RATE

There are wide variations in estimates of relapse rates in different regions. This is probably due to variations in the definition of relapse, proportions of previously dapsone-treated and untreated patients, range of skin smear positivity in MB cases and differing durations of follow-up. The risk of relapse is very low, both for PB and for MB patients after completion of MDT, and this is at least 10 times lower than with dapsone monotherapy.<sup>[1]</sup>

The WHO has estimated a risk of relapse of 0.77% for MB and 1.07% for PB patients 9 years after stopping MDT. Various other studies using person-years of observation estimate relapse rates varying from 0.65 to 3.0% for PB and 0.02 to 0.8% for MB leprosy.<sup>[1]</sup>

A retrospective study of data from the Central Leprosy Teaching and Research Institute, Chengalpattu, Tamil Nadu, included 3248 leprosy patients who completed the WHO MDT during the period 1987–2003.<sup>[5]</sup> The overall relapse rates for MB and PB leprosy were 0.84 and 1.9%, respectively, whereas the rates for person-years of follow-up were 0.86 and 1.92/1000, respectively. The majority of relapses occurred in the first 3 years after release from treatment. If an individual does not relapse within the first 5–6 years, his/her risk of relapsing is negligible.

In a recent retrospective analysis of the relapse rate in China after 24 months of WHO MB-MDT for 2374 MB patients who were followed-up for a mean duration of 8.27 years per patient, five patients with relapse were identified with an accumulated relapse rate of 0.21/1000 person-years, which is quite low.<sup>[6]</sup>

Surprisingly, there were no confirmed relapses in 502 patients who completed fixed-duration MDT in the AMFES (ALERT MDT Field Evaluation Study) cohort, a descriptive study of leprosy in Ethiopia,<sup>[7]</sup> in

a follow-up period of up to 8 years after completion of treatment, even in the 57 cases with an initial average BI  $\geq 4.0$ , 20 of whom have been followed-up for more than 5 years after ceasing MDT. This again indicates that the relapse rate after MDT is low.

## MICROBIOLOGICAL ASPECTS

The conventional method of confirming activity or relapse in an infectious disease is demonstration and/or culture of the etiologic agent. These methods unfortunately have limited utility in leprosy because of the difficulty in demonstrating bacilli in PB cases and absence of a method of *in vitro* cultivation of *M. leprae*. Unlike PB leprosy, where the criteria for relapse depend heavily on clinical features, bacteriological parameters are useful in MB leprosy.

Reappearance of positivity for AFB after the case has become negative has been considered as a feature of relapse in both PB and MB cases. Persisting high BI or increase in BI are also important parameters for diagnosing relapse in MB leprosy. BI persisting at the same level, an increase in BI of 2+, appearance of active lesions with high BI or BI becoming greater than what it originally was in the pre-existing lesion are some of the criteria for diagnosing relapse. However, an increase in BI of even 1+ should be considered as adequate supporting evidence for diagnosing relapse in patients who had earlier become negative or were showing a downward trend in BI after MDT.<sup>[8]</sup>

A number of *in vivo* and *in vitro* techniques are available for monitoring the progress of treatment in leprosy, which can also be used as additional objective criteria for confirming relapse. *In vivo* techniques that measure viability include the use of mouse foot-pads for cultivation of *M. leprae*. *In vitro* measures of viability include morphological index, fluorescent diacetate ethidium bromide (FDA-EB) staining, laser microprobe mass analysis (LAMMA), adenosine triphosphate measurements and macrophage-based assays. Molecular techniques include DNA and RNA targeting probes and gene amplification by polymerase chain reaction (PCR).<sup>[8]</sup>

A study conducted at the Schieffelin Leprosy Research and Training Center, Karigiri, India, tested biopsy samples of lepromatous patients who completed 12 and 24 months of MB-MDT for viable *M. leprae* by mouse foot-pad inoculation.<sup>[9]</sup> None of the skin or nerve

biopsies from patients who completed 24 months of MDT showed any growth whereas a small percentage (3.3%) of patients with a high BI were found to harbor viable bacteria in the skin after 12 doses of MDT. These patients need to be followed-up for a longer period to ascertain whether or not they will relapse.

## IMMUNOLOGIC TESTS FOR RELAPSE

Although, there are no widely available serologic tests for leprosy other than in a research setting, various immunological tests may be useful for monitoring patients on chemotherapy as well as for confirming suspected cases of relapse. Lepromatous patients show a significant rise in titer of phenolic glycolipid (PGL) immunoglobulin (Ig) M antibodies during the time of relapse. Tuberculoid (TT)/borderline tuberculoid (BT) cases who relapse to borderline lepromatous (BL)/lepromatous lesion (LL) types may be detected by measuring anti-PGL-1 and anti-35 kD antibodies.<sup>[10]</sup> The dipstick assay for detection of anti-PGL-1 antibodies has been used as a simple tool for classification of patients and for identification of those patients who have an increased risk of relapse.<sup>[11]</sup> The natural disaccharide ND-O-Bovine serum antigen (BSA) enzyme-linked immunosorbent assay (ELISA) (ELISA using the ND of the phenolic glycolipid antigen of *M. leprae* linked to BSA as antigen) is another useful test both for screening for early infection with *M. leprae* and for predicting a relapse, particularly in cured MB patients.<sup>[12]</sup>

The Th1 and Th2 type of interleukin (IL) profile may be a useful method of identifying the type of relapsed leprosy. For example, when BL/LL patients relapse as TT/BT type, an upgradation of cell-mediated immunity is expected, in the form of a Th1 type of immune response, which consists of a rise in the levels of interferon (IFN)-gamma, IL-2 and IgG2 antibodies, in addition to a positive lepromin test. On the other hand, when TT/BT patients relapse to BL/LL types, a Th2 type of immune response is initiated, which should lead to a rise in IL-4, IL-5, IL-6, IL-10 and IgG1 production, a concomitant fall in IL-2 and IFN-gamma and lepromin negativity.<sup>[10]</sup>

It may be possible to differentiate reinfection from relapse by molecular typing of *M. leprae*, based on amino acid sequencing as well as to identify relapse at a very early stage using nucleic acid amplification techniques such as PCR.<sup>[10]</sup>

## HISTOPATHOLOGY

Regular skin biopsies and skin smears, at least once in 6 months, from representative lesions should be studied during the period of treatment and the following 5 years after achieving negativity.

### *Histopathology of relapsed lesions in MB leprosy<sup>[13]</sup>*

As LL resolve under treatment, increasing number of macrophages become foamy, Schwann cells show foamy change, there is reactive proliferation of the perineurium and increasing fragmentation and granularity of the AFB in the granuloma are seen. The granuloma gradually resolves, without any residual fibrosis or scar formation, and there is fibrous replacement of the perineurium and hyalinization of the nerve parenchyma. Foam cell collections are known to persist for long periods in the tissues, many years after the skin smears have become negative. A mild non-specific chronic inflammation characterized by small focal collections of lymphocytes around skin adnexa can also persist in resolved LL lesions for several years.

In the early phase of relapse, small and large foci of newly arrived spindle-shaped macrophages with a pink granular cytoplasm are identified along with a few small clumps of persisting foamy macrophages. Solid staining AFBs reappear in skin smears and biopsy specimens in patients who may or may not have become completely smear negative. Once the lesion is well established, the foamy change becomes obscured by collections of spindle-shaped and immature macrophages. Skin adnexa are markedly atrophic and scanty, and dermal nerve bundles are few and show perineurial thickening and fibrosis. Macrophages, Schwann cells and endothelial cells are packed with solid-staining AFBs.

Occasionally, there is infiltration by polymorphs and it is also not uncommon to see LL patients relapsing with upgrading reactions in the form of BL or, rarely, BT lesions.

Lesions of BL resolve much faster than polar LL cases and become bacteriologically negative much earlier. Histopathologically, BL lesions leave behind a few focal collections of mononuclear cells around the skin adnexa and foam cells are not usually seen. Relapses in BL manifest as LL, BL or, rarely, as BT.

### *Histopathology of relapsed lesions in PB leprosy<sup>[13]</sup>*

Lesions in BT and TT leprosy are the result of a hypersensitive granulomatous response to the antigens of *M. leprae* and are not directly due to the presence of *M. leprae*. With treatment, there is reduction in the size of the granuloma without any fibrous replacement of the skin adnexa. Dermal collagen is destroyed during the inflammatory process, leading to an atrophied and wrinkled appearance of the healed skin lesions. Nerves undergo perineurial and intraneural fibrosis. *M. leprae* get buried alive in these nerves and also in the arrector pili muscle cells, thereby serving as a focus for relapse.

The difficulty that arises in PB cases is the differentiation of relapse from reaction. Features that suggest a reaction include edema around the granuloma, dilated lymphatics and proliferating fibroblasts throughout the dermis. A true relapse can be detected histopathologically only after recording complete histological resolution of the lesion, which may take years. Relapse indicates that the bacilli have survived despite antileprosy therapy and have multiplied and released antigens to produce fresh granulomas. This manifests as the appearance of solid-staining organisms inside the fibrosed nerve bundles (where there were none earlier) and the reappearance of a granuloma at the site of the original lesion. This granuloma usually begins as a small focus of lymphocytes and epithelioid cells, which often starts in fibrosed nerve bundles or arrector pili muscle cells. Once the granuloma becomes well established, it grows and involves large portions of the dermis, becoming indistinguishable from the original lesion. Therefore, in PB patients, regular 6-monthly biopsies showing disappearance of the granuloma will confirm "cure" and reappearance of the granuloma will identify "relapse." Rarely, PB cases will relapse as MB, and this is usually due to misdiagnosis of the spectrum of disease and the resultant inadequate treatment in the first place.

## RELAPSE INTERVAL

Relapse interval is otherwise known as incubation period of relapse.<sup>[14]</sup> It is different with monotherapy and MDT.

### **Dapsone monotherapy:**<sup>[14]</sup>

Fifty-five to 57% of relapses occurred within

1. 3 years in non-lepromatous

2. 5 years in borderline
3. 6 years in lepromatous MDT.<sup>[14]</sup>
  1. PB, same as with monotherapy
  2. MB, 9 years (median)

The implication of these figures is that PB patients should be under surveillance for at least 3 years and MB patients for 9 years so that a majority of the relapses can be detected.<sup>[14]</sup>

## **PREDISPOSING FACTORS FOR RELAPSE<sup>[14]</sup>**

### *Persisters*

Persisting organisms or “persisters” consist of permanently or partially dormant organisms that have the capacity to survive in the host despite adequate chemotherapy. They have been identified in immunologically favorable sites such as dermal nerves, smooth muscle, lymph nodes, iris, bone marrow and liver. These organisms, which are responsible for relapse, are present in about 10% of the MB patients, and their proportion may be higher in cases with higher BI.

### *Inadequate therapy*

This is usually the result of clinical miscategorization of MB leprosy with few skin lesions as PB cases, who receive 6 months of MDT instead of 12 months, initially respond to treatment and eventually relapse.

### *Irregular therapy*

Irregularity in ingesting self-administered clofazimine and dapsone either due to an irregular supply of drugs or non-compliance on the part of the patient, effectively resulting in a scenario of rifampicin monotherapy. This will lead to rifampicin resistance and subsequent relapse.

### *Monotherapy*

The relapse rate is high among patients who have received dapsone monotherapy and did not later receive MDT. This is also due to the development of resistant organisms.

### *High initial BI*

Patients who have a high BI initially are at greater risk of relapse after fixed duration MDT compared with patients who are smear negative or have a low BI.

### *Number of skin lesions and nerves*

The number and extent of lesions including nerve lesions, when multiple, i.e. more than five and covering

three or more areas of the body, correlate with a higher relapse rate. Mycobacterial antibodies have been found in TT leprosy with a large number of lesions and in BT leprosy with more than 10 lesions. Because this is evidence of a fairly large number of organisms, these patients may not be truly PB and treatment with two drugs for 6 months might be considered inadequate for these patients.

### *Lepromin negativity*

Borderline patients with a positive lepromin test have been observed to have a lower relapse rate than those with a negative response.

### *Human immunodeficiency virus (HIV) infection*

Although leprosy has now been reported presenting as an immune reconstitution disease among patients commencing highly active antiretroviral treatment, there is no evidence as yet to suggest an increased risk of relapse in patients with HIV coinfection.

## **CLINICAL FEATURES<sup>[14,15]</sup>**

**Age:** In MB cases, relapse is more common in the older age groups. PB leprosy with single skin lesions is more common in younger age groups and relapse is less common in this group.

**Sex:** Relapses are more common in males, possibly because of the higher prevalence of leprosy in males. Relapses are seen in females in the setting of pregnancy and lactation.

### **Relapse in PB leprosy**

- a) **Skin lesions:** Previously subsided skin lesions show signs of renewed activity, such as infiltration, erythema, increase in extent and appearance of satellite lesions. Often, there is an increase in the number of lesions as well.
- b) **Nerves:** New nerves may become thickened and tender, accompanied by an extension of the area of sensory loss and an insidious onset of motor deficit. Patients may complain of aches and pains along the peripheral nerves with or without evidence of nerve damage. Relapse may occur only in nerves without skin involvement (neural relapse) and there may be a change in the spectrum of disease on relapsing.

### **Relapse in MB leprosy**

- a) **Skin lesions:** Relapse may present as localized areas of infiltration over the forehead, lower back, dorsa of hands and feet and the upper part of the buttocks.

Soft, pink and shiny papules and nodules may be found at these sites, with or without a background of infiltration. Papules may enlarge to form plaques. Subcutaneous nodules may appear on the posterior arms and anterolateral thighs. They feel like peas in a pod and increase in size with time. Skin smears from the overlying skin may be negative; hence, the scalpel should be plunged deep into the core of the nodule while taking smears.

- b) Nerves: Nodular swellings may occur along the course of cutaneous nerves and peripheral nerve trunks in addition to fresh nerve thickening and/or tenderness, with insidious loss of function.
- c) Ocular lesions: Cases with pre-existing eye involvement may relapse with iris pearls or, rarely, lepromata.
- d) Mucosal lesions: Papular or nodular lesions may be seen on the hard palate, inner lips and glans penis.

**DIFFERENTIAL DIAGNOSIS**

Differences between erythema nodosum leprosum (ENL) and relapsed fresh papules and nodules<sup>[14]</sup>

Papules and nodules that occur as part of relapse in the MB spectrum should be differentiated from ENL nodules. The most important point of difference is that ENL nodules are tender and evanescent, unlike lepromatous nodules. Additional differences are listed in Table 1.

**Differences between reversal reaction and relapse**

It is often a diagnostic dilemma to differentiate true relapse from a late reversal reaction in a PB case.<sup>[14,15]</sup> Many studies on PB leprosy show falsely high relapse rates, possibly because of the inclusion of cases that are probably reactions and not really relapses. Some of the features that will help in differentiating these two conditions are given in the Table 2.

**Relapse vs. resistance**

Drug resistance is an emerging problem in leprosy worldwide, owing primarily to the chronicity of the disease and the long duration of treatment required.<sup>[14,15]</sup> Drug resistance may be primary, wherein lepra bacilli are resistant to the concerned drug from the onset itself, or secondary, wherein resistance develops as a result of mutant bacilli surviving in the setting of irregular therapy or monotherapy. Dapsone resistance is the most common, owing to the earlier concept of dapsone monotherapy. Rifampicin resistance occurs in the setting of irregular therapy. Clofazimine resistance is very uncommon. Although mouse foot-pad studies are recommended for confirmation of drug resistance in leprosy, these facilities are not available freely, forcing clinicians to rely on clinical features alone. Drug resistance may itself be a reason for relapse and it is important to differentiate the two, as outlined in the Table 3.

**Relapse vs. reactivation**

Reactivation of lesions occurs due to treatment failure, i.e. premature termination of treatment or gross irregularity in treatment either due to non-compliance or irregular supply of drugs.<sup>[14,16]</sup> Reactivation occurs soon after subsidence of the disease while relapses occur after complete and sustained subsidence of the disease.

**Relapse vs. reinfection**

Recurrence of disease in a cured case may be due to reinfection.<sup>[14,16]</sup> Reinfection is an extremely difficult condition to prove, especially in an endemic area. When cured, leprosy patients continue to live in and around the leprosy sanatoria. In hyperendemic areas, they may develop the disease again due to exogenous infection. Also, patients get cured not only by the killing of germs by bactericidal drugs but also by the added immunity the patients develop subsequent to the treatment. This is supported by the fact that even

**Table 1: Differences between erythema nodosum and relapsed papules and nodules**

Feature	ENL	Relapsed papules and nodules
History of therapy	Episodes during therapy in LL, LLs and, rarely, BL	After completion of therapy, during surveillance in borderline borderline leprosy (BB), BL, LLs, LL and, rarely, BT
Onset	Sudden	Insidious
Constitutional symptoms	Present	Absent
Physical signs	Nodules are tender, warm, erythematous, blanchable on pressure and superficially located	Non-tender, not warm, pink, do not blanch, involve full thickness of skin
Skin smears	Fragmented AFB, polymorphs	BI > 2+, long solid staining AFB, globi +
Course	Change from red to bluish and dusky, evanescent – subside within 48–72 h	Pink changes to skin colored, consistency changes from soft to firm, in months

**Table 2: Differences between reversal reaction and relapse**

Feature	Reversal reaction	Relapse
Time course	Usually within 6 months of release from treatment; in recurrent reactions, up to 2 years	1 year or more after release from treatment
Type of disease	BT, BB, BL	All types
Skin lesions	Increased erythema, swelling, tenderness on pressure, succulent consistency; upward or downward change in the spectrum may occur; edema of hands/feet	Increase in extent and number of lesions, no tenderness, rubbery consistency; edema of hands and feet rare
Ulceration	Seen in severe reactions	Not seen
New lesions	Few, same morphology	Many
Nerves	Acute painful neuritis; nerves exquisitely tender; nerve abscess; sudden paralysis of muscles and increase in extent of sensory loss	New nerves involved; no spontaneous pain; tenderness on pressure; sensory and motor deficits slow and creeping
Skin smears	Continued decrease in BI. Granularity of bacilli increases in reactions	AFB positivity may occur in skin smear-negative patients
Lepromin test	Progressively positive Fernandez reaction in BL and BB upgrading to BB and BT, respectively	Corresponds to the type of relapsed leprosy
Response to systemic steroid	Complete subsidence of lesions in 2–4 weeks; remain subsided with 2-month therapy	No response or partial response

**Table 3: Drug resistant leprosy versus relapse**

Drug-resistant leprosy	Relapse
Because of primary or secondary drug resistance	Mainly due to persists
Initial amelioration followed by halt or worsening	Recurrence after release from MDT
Appearance of new lesions	Reappearance of lesions over old lesions
Patient downgrades	Patient rarely downgrades

an LL patient is able to actively dispose off the dead bacilli. Hence, a treated lepromatous case is not truly immunoincompetent and the risk of reinfection is not high. When reinfection does occur, the incubation period is bizarre and fresh skin and nerve lesions do not correspond to the original lesions.

## DIAGNOSIS

The diagnostic criteria for relapse are:<sup>[10,14]</sup>

### *Clinical criteria*

- increase in size and extent of existing lesion(s)
- appearance of new lesion(s)
- infiltration and erythema in lesions that had completely subsided
- nerve involvement (thickening or tenderness)

### *Bacteriological criteria*

Positivity (in a smear-negative patient) at any site in skin smears for AFB at two examinations during the period of surveillance is diagnostic of relapse. In

patients with a positive BI, if BI increases by 2+ over previous smears at any two sites and continues to be so at two examinations, it is diagnosed as relapse, provided the patient has ingested 75% of the drugs.

### *Therapeutic criteria*

This is useful when reversal reaction is suspected. The patient may be treated with prednisolone (reaction dose being around 1 mg/kg/day), after which a reversal reaction should subside completely in 2 months. If symptoms do not subside or only partially subside or lesions persist or increase under the cover of steroid, relapse should be suspected.

### *Histopathological criteria*

This includes the reappearance of granuloma in PB cases and increased macrophage infiltration with solid-staining bacilli and increasing BI in MB cases.

### *Serologic criteria*

In LL cases, the measurement of PGL-1 IgM antibodies is a good indicator of relapse.

The first three criteria are sufficient to make a diagnosis of relapse; criteria 4 and 5 are additional and may be used wherever facilities are available.

## TREATMENT

Relapsed cases of leprosy should be identified and put back on chemotherapy as soon as possible to prevent further disability and transmission of infection.<sup>[17]</sup>

Factors that should be considered in choosing an appropriate regimen are:

1. Type of leprosy (PB or MB)
2. Previous treatment
3. Drug resistance

**Type of leprosy**

PB cases usually relapse as PB, and MB cases as MB. However, PB cases occasionally relapse as MB and such cases should receive MB-MDT.

**Previous therapy**

- a) Patient previously treated with dapsone monotherapy – standard WHO MDT is sufficient.
- b) Patient previously treated with clofazimine monotherapy – standard WHO MDT is sufficient (clofazimine resistance is extremely rare).

**Drug resistance**

Patients with known or suspected drug resistance pose a treatment problem only in the case of rifampicin resistance, which is rare. MB patients who have received rifampicin as part of MDT are not at any significant risk of rifampicin resistance, unless they were infected with fully dapsone-resistant bacilli and either did not take their clofazimine or were not given another effective drug. Dapsone resistance occurs in the setting of prior dapsone monotherapy and such cases respond well to standard WHO MDT. Clofazimine resistance is extremely rare, if at all it occurs, and these cases also respond to the other two drugs in the standard WHO MDT.

Although drug resistance ideally is determined using

the mouse foot-pad or other techniques, relatively few leprosy centers have such a facility available. Thus, the decision on drug resistance most often is based on clinical information alone. Recommended treatment regimens are given in Table 4.

**Failure to respond to therapy**

This group includes patients who do not respond as expected in terms of clearance of skin lesions and bacilli after therapy is discontinued or patients who actually show disease progression during therapy. The former group contains potential relapse cases, but great care must be taken to rule out reaction and/or slow clearance of lesions and bacilli as a cause of poor response.

The WHO defines a “satisfactory result from MDT” in a patient who complies with treatment as – one in which, after the start of therapy, bacilli begin to clear in MB cases and lesions generally, although not necessarily, rapidly improve in both PB and MB cases. Clearance of lesions is related more to the patient’s immune response than to antileprosy treatment; all lesions and bacilli should eventually clear even though clearance may be incomplete at the time treatment is discontinued.<sup>[17]</sup>

MDT regimens being used in the United States [Table 5] are more robust than the ones being recommended in developing countries by the WHO. Although studies show that relapse rates are very low after WHO MDT, the fact remains that relapses do occur. There is a possibility that more relapses in leprosy may develop if the WHO accepts uniform

**Table 4: Recommended treatment regimens**

Resistance	Scenario	Treatment
Relapse with <i>M. leprae</i> sensitive to all standard drugs	Relapse after a course of MB-MDT	Retreatment with WHO MDT depending on the type of disease (PB or MB-MDT)
Relapse with dapsone-resistant <i>M. leprae</i>	Relapse after previous “cure” with dapsone monotherapy	Standard WHO MDT
Relapse with rifampicin-resistant or rifampicin- and dapsone-resistant <i>M. leprae</i>	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 or minocycline 100 mg daily or clarithromycin 500 mg daily, followed by: ofloxacin 400 mg daily or minocycline 100 mg daily for the remaining 18 months

**Table 5: Multidrug therapy regimens in the United States of America<sup>[18]</sup>**

Type of leprosy	Dosage of drugs *CLF may be added	Dapsone 100 mg after MDT for
Paucibacillary (I, TT, BT)	Dapsone 100 mg daily + rifampin 600 mg daily for 6 months	3 years (I, TT) 5 years (BT)
Multibacillary (BB, BL, LL)	Dapsone 100 mg daily + rifampin 600 mg daily for 3 years	10 years (BB) Lifelong (BL, LL)

MDT. Unfortunately, it is not practical to introduce regimens like those in the United States on a large scale in a resource-poor setting like India. However, clinicians may use their judgement and tailor treatment regimens for individual patients wherever practicable. In selected cases, longer regimens similar to those used in the United States may be useful.

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## Multiple choice questions

1. The WHO has estimated a risk of relapse of:
  - a) 1.07% for PB and 0.77% for MB leprosy.
  - b) 0.65% for PB and 0.02% for MB leprosy.
  - c) 3.0% for PB and 0.8% for MB leprosy.
  - d) 0.84% for PB and 1.9% for MB leprosy.
2. The correct statement regarding relapse among the following is:
  - a) Bacteriologic parameters are more useful in PB leprosy.
  - b) The diagnosis of MB leprosy relies on clinical features.
  - c) Both bacteriological and clinical features are useful in the diagnosis of relapse in PB cases.
  - d) The diagnosis of relapse in PB leprosy relies primarily on clinical features.
3. *In vitro* measures of viability of M. leprae include all except:
  - a) Morphological index.
  - b) FDA-EB staining.
  - c) LAMMA.
  - d) Titer of PGL-IgM antibodies.
4. Immunologic tests for leprosy include all except:
  - a) Macrophage-based assays.
  - b) PGL-IgM antibodies.
  - c) ND-O-BSA ELISA.
  - d) Lepromin test.
5. All of the following statements regarding histopathology of relapsing PB lesions are true except:
  - a) M. leprae in nerves and arrector pili muscle cells serve as a focus for relapse.
  - b) Reappearance of solid-staining organisms inside fibrosed nerve bundles.
  - c) Reappearance of a granuloma at the site of the original lesion.
  - d) There is edema around the granuloma.

6. Relapse interval after MDT is:
  - a) 8 years in MB cases.
  - b) 6 years in borderline cases.
  - c) 3 years in PB cases.
  - d) 2 years in BT cases.
7. The ideal period of surveillance (based on relapse interval) so that a majority of relapses can be detected is:
  - a) At least 6 years for PB patients.
  - b) At least 9 years for MB patients.
  - c) At least 2 years for PB patients.
  - d) At least 5 years for MB patients.
8. All the following statements regarding “persisters” in leprosy are true except:
  - a) Dormant organisms that have the capacity to survive in the host despite adequate chemotherapy.
  - b) Present in immunologically favorable sites such as dermal nerves, smooth muscle, lymph nodes, iris, bone marrow and liver.
  - c) Responsible for resistance to treatment.
  - d) Present in about 10% of MB patients.
9. The incorrect statement regarding clinical features of relapse in PB leprosy is:
  - a) Occurs within 6 months of release from treatment.
  - b) Previously subsided skin lesions show signs of renewed activity.
  - c) New nerves may become thickened and tender.
  - d) Relapse may occur only in nerves without skin involvement.
10. The recommended treatment for relapse cases with rifampicin resistance is:
  - a) Dapsone monotherapy.
  - b) Standard WHO MDT.
  - c) Standard WHO MDT without rifampicin.
  - d) A regimen of clofazimine combined with ofloxacin/minocycline/clarithromycin.

1-a, 2-d, 3-d, 4-a, 5-d, 6-c, 7-b, 8-c, 9-a, 10-d  
**Answers**

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