

Current problems in Leprosy

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Major achievements have been made since 1981, particularly with the intervention of the WHO, in reducing the global burden of leprosy. Between 1985 and 2005, more than 14 million leprosy cases were diagnosed and completed treatment with multi drug therapy. The number of countries reporting prevalence rates above one per 10,000 population has been reduced from 122 in 1985 to 9 at the beginning of 2004.

Even with these achievements, many problems remain: Problems relating to the diagnosis and classification of leprosy; the necessity of a biopsy and /or smear in each case. There is no controversy that all diagnosed leprosy patients require multi drug therapy. Even here the length of treatment, the mode of administration and the end point of treatment are questioned. The use of immunotherapy in treatment is still not established.

Relapses after treatment are not too well documented. With increasing drug resistance relapses are bound to occur and increase. This creates the need for the constant search for newer drugs and drug regimes.

Lepa reactions and their management are a constant source of concern. The occurrence and the recurrence of reactions long after the completion of therapy should call for systems of long term follow up of patients. The current WHO regime for the management of reactions seems inadequate in a number of patients. This leads to the recognition and adequate management of the disabilities in leprosy – still a stigma of leprosy.

Toxic reactions to drugs must surely be in excess of the reported figures to the WHO. Liver toxicity, dapsone hypersensitivity reactions remain causes of concern. Haemolytic anaemia to some degree seems inevitable with dapsone therapy.

The diagnosis of leprosy

The proposal that leprosy can be diagnosed by the presence of an anaesthetic lesion alone does not pass critical assessment. Even though 70% of lesions have

reduced sensation, the 30% of non anaesthetic lesions occur in MB disease^{1,2}. However the addition of enlargement of peripheral nerves with signs of peripheral nerve damage, the detection of acid-fast bacilli at the lesions, and the evidence of pathology from a skin biopsy³, are all surely not essential for a diagnosis of leprosy?

Is biopsy always necessary? This question has to be asked in a set up where medical practitioners are expected to diagnose and treat leprosy. When clinical signs are definite this probably is an unnecessary procedure with sometimes non-conclusive results in pauci bacillary (PB) lesions. A split skin smear is desirable when adequate expertise for staining and interpretation and sterility is available, especially in multi-bacillary patients (MB). This facility is not available in Sri Lanka except in the very large hospitals. It is necessary that microscopists be given the training and expertise to perform split skin smears in all major hospitals. Any way this would diagnose and quantify the bacillary index, only in some of the MB patients. The diagnoses of PB lesions in paediatric patients are a special problem, since sensory testing is not always reliable. Should this mean that all these children will have to be subjected to an invasive biopsy procedure in a tertiary care hospital? Would not a review of the lesions in a few months be a more rational method? The diagnosis should be established when the signs and symptoms are clear and unequivocal. If there is the slightest doubt, the patient should be kept under observation until further evidence confirms the diagnosis³.

Hypo pigmented, well defined patches with a significant loss of sensation on them, with or without an associated thickened and tender peripheral nerve is termed as PB or tuberculoid leprosy patches. It is when the patch is ill demarcated and the sensory impairment is not clearly demonstrable that the diagnosis becomes difficult. Some clinical help has been suggested⁴. These include "Stretch enhancement" where stretching the edges of the patch will show a well defined border, "tap sign" when tapping on a

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patch overlying a bone will elicit a sharp pain, "across the patch testing" and "sensory testing with the point of a folded paper"^{4,5}.

The WHO classification of counting the patches on the whole body and classifying as PB where 1 to 5 patches are found and as MB where more than 5 patches are found is simple effective and useful in the situation where all medical practitioners and paramedical workers have to diagnose leprosy⁶. In a well-documented study it was found that the WHO operational classification, for sensitivity and specificity of diagnosis was 88.6% and 86.7% respectively⁷.

This however leaves many questions. The clinical aspect of MB leprosy of erythematous or skin coloured papules, nodules plaques and macules, where many of them will not have sensory loss, leaves these lesions marginalized. Should the large size of a patch especially with an erythematous raised border be considered as criteria for a diagnosis of MB? The status of indeterminate and pure neural leprosy is also not handled. By leaving out the borderline group the possibility of more reactions in this group will also be overlooked. The fact that those lesions with a high bacillary count needs special attention is also forgotten.

Treatment of leprosy

There is no controversy that all patients need multi drug therapy as recommended by the WHO⁸. However controversies still exist regarding the length of therapy for MB patients, the mode of dispensing of treatment, relapse rates and the use of immunotherapy.

Although the composition of the MDT regimen for MB leprosy has remained unchanged, the duration of treatment has been progressively shortened, from 24 months or smear negativity, whichever takes longer⁸, to 24 months irrespective of smear results⁹ and then to 12 months⁶. The efficacy of the 12 month regime has been shown in some studies¹⁰. However there are reports of the possibility of the existence of a higher risk group of MB patients who are more prone to relapses on this regime^{11,12}.

What is the end point of treatment? The WHO considers it the end of the WHO recommended regime⁶. Some would want all clinical lesions to disappear. Various studies have shown that 2-44% of PB patients have clinical lesions at the end of 6 months¹³. Most of these would disappear with time. But do all lesions disappear? Should we look for disappearance of bacilli from smears in MB Leprosy? Bacillary clearance is a slow process and may take 24 or more months (median 53.5 months)¹⁴. Would histological inactivity be an index of cure? The histological appearances of leprosy also take time to clear. At the end of 6 months of therapy for PB leprosy 32% of the

lesions still showed histological activity¹⁵, even though some had even shown a disappearance of lesions.

At this point of time the WHO regime is recommended, since they are supported by 20 years of experience¹⁶. It would therefore be prudent to end therapy at the end of the WHO regimen, but follow up the patient to look for disappearance of lesions and the appearance of new ones (relapses).

Relapses

WHO data collection between 1981-1993 presents a very favorable picture. The relapse rates were 1.09% per 1000 person years for PB patients and 0.74 per 1000 person years for MB. Figures from India show that a follow up of 20 years in MB patients gave a relapse rate of .07 per 1000 patient years with treatment to smear negativity¹⁷. In a large study from West Bengal India, figures similar to those of the WHO were obtained¹⁸. However more studies of relapses of leprosy following treatment are required, particularly since the clinical impression is that there are more relapses than the numbers reported.

Resistance to the standard drugs is being increasingly reported. Japanese studies of 88 bacterial isolates from patients in Indonesia, Pakistan and the Philippines using PCR DNA sequences for resistance to Quinolones, Rifampicin, and Dapsone showed that 11 bacterial isolates were resistant to 2 of these drugs and 2 of them to all 3 drugs¹⁹. Hence new drugs and established alternative regimes are essential. The demonstration that Ofloxacin, Perfloracin and Levifloxacin, together with Minocycline and Clarithromycin were effective in the treatment of leprosy in the early 1990's was a great relief. Newer drugs such as Moxifloxacin and the most effective Rifapentine in 1999 added further options and newer drug regimes are being tried. It was shown that a single dose of Rifampicin, Ofloxacin and Minocycline was marginally less effective for single macular PB leprosy than the 6 months PB regime²⁰. However the use of this combination fully supervised once per month for MB leprosy lesions has shown a similar response to the 24 month standard regime²¹. In a 4 week daily regime of Rifampicin and Ofloxacin in both MB and PB patients a high relapse rate was noted. Trials with Moxifloxacin and Rifapentine are under way.

A trial of a drug regime of all 3 standard drugs for both MB and PB patients for a period of 6 months recommended as a trial by the WHO²² has been much criticized for inadequately treating MB leprosy and over treating PB leprosy²³. However the trial has an in built period of 5 years of follow up and should show inadequacies if they exist. It will be interesting to see the effect on reactions of leprosy on this regime, due to the addition of Clofazimine to the PB regime.

Indian and Venezuelan studies though small suggest that the addition, of BCG 6 monthly or the Mw (killed bacillus) monthly, achieved bacterial clearance earlier, that reactions and relapses were reduced and histological clearance was achieved earlier²⁴. Further large studies are needed to confirm these findings.

Lepra reactions

Reactions of leprosy are a major problem in leprosy control. In a retrospective study from Sri Lanka reactions occur in 3% of PB patients and 19.2% of MB patients²⁵. The figures for a 15 year study in India were considerably higher; accounting for over 30.9% of reactions in 2600 patients²⁶. In this study 64.3% of patients with Erythema Nodosum Leprosum (ENL) reactions had recurrent episodes, which continued for up to 8 years after the start of treatment. Female gender, widespread disease with MB, and a high bacillary index were identified as risk factors for the development of ENL reactions.

Nerve damage leading to impairments and permanent disability is a feared sequelae of leprosy. Both type 1 and type 2 Erythema nodosum leprosum (ENL) reactions lead to such damage²⁷. In type 1 reactions the nerve trunks at specific sites may become swollen and tender, and may show deterioration of function, which is usually gradual, taking weeks or months to become irreversible. Occasionally, severe damage may occur overnight^{27,28}. Skin involvement frequently accompanies nerve involvement, but can also precede or follow the nerve damage^{26,29}. There is increased inflammation of preexisting skin lesions. Hypopigmented or only slightly erythematous macules become red and swollen, form plaques, and occasionally undergo ulceration. In Type 2 reactions (ENL) the nerve damage may take years to develop. The patients are very ill with fever myalgia and arthralgia. New erythematous lesions occur on various parts of the body. Reactions must be diagnosed early and treated appropriately if permanent disability is to be avoided.

Treatment of reactions

The WHO recommended treatment for reactions include the use of prednisolone at a starting dose of 40mg per day reduced over 12 weeks for both type 1 and type 2 reactions⁶. This regime usually gives excellent results for type 1 reactions. However, 3 months later, recurrence of nerve damage is common³⁰. The use of longer courses of prednisolone, with the critical low end of the effective dose being 15-20mg per day has been advocated²⁷. The addition of azathioprine at a dose of 3mg/Kg/day with a 8 week reducing dose of prednisolone was found effective³¹.

Ciclosporin has also been used to treat reactions but the patients relapsed when the drug was withdrawn. When during an otherwise effective anti-reaction treatment, one or two nerves are not responding, a nerve decompression operation should be considered under steroid cover, within 3 months of onset of the reaction^{32,33}.

ENL reactions are much more severe reactions with systemic symptoms and effects on other organ systems. These are episodic in nature²⁷ and recurrences are common and these can continue for up to 8 years after the start of treatment²⁶. For the treatment of ENL reactions prednisolone therapy has been very effective. However the WHO regime⁶ dose of 40mg is often not high enough and the period of use leads to numerous side effects and steroid dependence. An initial dose 1-2mg/Kg body weight with a shorter duration of therapy for 4 weeks has been suggested, with re-treatment at a higher dose if relapses occur^{34,27}. Clofazimine at a higher dose of 300mg/day for long periods of 2 months or more has been suggested as an adjuvant to prednisolone, and the steroids can be gradually withdrawn under the protective umbrella of clofazimine^{34,35,36,37}. Pentoxifylline, a TNF- α inhibitor, at a dose of 400 mg tds, has been used over a period of 4 months and tapered down as a successful treatment of ENL reactions³⁸. In a report of a few patients the use of intravenous dexamethasone pulse therapy given at 4 week intervals, together with azathioprine daily and a gradual reduction of the dose of prednisolone proved effective³⁹. Colchicine has been shown to have some effect on ENL⁴⁰, but the results are not as impressive as those claimed in the initial trials. Thalidomide 300-400 mg daily is better than even steroids in controlling ENL and is the drug of choice for young men with severe ENL^{16,41}. The use of thalidomide in women, while on contraceptive use, is still a cause of great concern for the physician and the patient in view of its known embryopathic complications. The clear possibility of thalidomide neuropathy has also to be considered⁴². Therefore there is the need for strict guidelines for its use in ENL reactions.

Nerve impairment in leprosy

Nerve impairment is the most severe sequelae of leprosy. In a study from Bangladesh⁴³, visible deformities increased from 4% at enrolment to 7% after 8 to 10 years follow up of PB patients. MB patients were found to be at a higher risk. During treatment those with a higher rate of nerve impairment were found to be those with MB leprosy and those with pre-existing impairment of nerve function. Delay in presentation for treatment of leprosy was associated with increased nerve function impairment at presentation⁴³.

In a different approach, the TRIPOD trials (Trials in the Prevention Of Disability) used randomized,

multi-center, double blind, placebo-controlled trials designed to investigate the prevention and treatment of nerve damage in leprosy by using corticosteroid therapy. The TRIPOD 1 study found that MB patients started on MDT and prednisolone or placebo for 4 months, had significantly fewer reactional episodes in the prednisolone treated group, but that the effect did not last once the therapy was stopped⁴⁴. The very early treatment of sensory loss as detected by monofilaments, neither improved the touch sensibility, nor reduced the risk of leprosy reactions or nerve function impairment beyond the initial 4-month treatment phase⁴⁵. The use of a standard prednisolone regime did not demonstrate an additional improvement in nerve function in patients with untreated nerve function impairments. However improvement of nerve function at 12 months in both prednisolone treated and the placebo group, in about 50% of patients. Spontaneous recovery of nerve function appears to be a common phenomenon in leprosy⁴⁶.

Nerve impairments lead to disabilities and these can occur even after therapy is completed. This is still a stigma of leprosy. The result of lack of active surveillance and follow up after the end of therapy will lead to increase of deformities and the lack of care for these patients. The vertical program now being used with diagnosis and care at the peripheral practitioner level will increase this risk.

The patient's self-awareness of areas of anesthesia is crucial so that damage is minimized. Studies of self-care show a reduction in hand and foot ulcers when patients are trained⁴⁷. The provision of ulcer care kits, special shoes or sandals, appliances for the management of foot drop and wrist drop and the need for surgery for contractures, foot drop, lagophthalmos, are all part of the long term programme for the management of disabilities.

The problem of adverse reactions to drugs

The number of adverse reactions to dapsone and rifampicin reported has been very low⁴⁸. In practice the problems of hepatitis and dapsone sensitivity syndrome are not frequently encountered. Haemolysis due to dapsone is present even in the presence of normal values of Glucose-6-dehydrogenase. In a poor population with low values of haemoglobin this can lead to symptoms. Studies of the frequency of adverse effects and guidelines as to their care are essential.

The diagnosis of a steady number of new cases even after elimination targets are met indicates that sustainable leprosy control programmes should be maintained and improved. In Sri Lanka about 80% of the new leprosy patients are being detected and treated by dermatologists. It is encouraging that the

leprosy control programme in Sri Lanka is recognizing this and that they hope to utilize the dermatologists in further training programmes and use the existing dermatology facilities as referral centers for problems encountered in diagnosis and management of patients.

The occurrence of childhood leprosy and the relative increase of MB patients remain concerns. Strategies for the eradication of leprosy such as total integration of leprosy into the general health services must be adjusted to each country and a system for the closer supervision and long term follow up of patients completing therapy is essential.

References

1. Report of the International Leprosy Association Technical Forum. *Int J Lepr Other Mycobact Dis* 2002; 70 (suppl): S1-S62.
2. WHO. Expert Committee on Leprosy, 7th Report, 1998: 1-43.
3. World Health Organization, A guide to leprosy control 2nd Edition 1988: 19, Geneva.
4. Kumarasinghe Prasad. Some clinical signs useful in difficult cases of tuberculoid leprosy. *Int J Dermatol* 2001; 40: 299-304.
5. Kumarasinghe SP, Kumarasinghe MP, Amerasinghe UJ. *Int J Lepr Other Mycobact Dis* 2004; 72: 278-83.
6. World Health Organization Expert Committee on Leprosy, 7th report. WHO technical report series No. 874. 1998, Geneva.
7. Norman G, Joseph G, Richard J. Validity of WHO operational classification and value of other clinical signs in the classification of Leprosy. *Int J Lepr Other Mycobact Dis* 2004; 72: 278-83.
8. WHO study group. Chemotherapy of leprosy for control programmes. WHO Technical Series no. 675. World Health Organization. 1982. Geneva.
9. WHO study group. Chemotherapy of leprosy, WHO Technical Report Series no. 847. World Health Organization, 1994, Geneva.
10. Sales AM, Satroza PL, de Costa Nery JA, Duppre NC, Sarno EN. A comparative study between 12 months and 24 months dose therapeutic regimes for multibacillary patients. *Int J Mycobact Other Dis* 2004; 72: 320-23.
11. Ji B. Deos there exist a subgroup of patients at a greater risk of relapse after MDT? *Lep Rev* 2001; 72: 3-7.
12. Report of the International Leprosy Association Technical Forum. *Lep Rev* 2002; June (suppl).
13. Lockwood DN. Leprosy elimination: a virtual phenomenon or a reality? *BMJ* 2002; 324: 1516-18.
14. Kumar A, Girdhar A, Girdhar BK. Pattern of bacillary clearance in MB leprosy patients with multi drug therapy. *Acta Leprol* 2003; 12: 123-28.

15. Matthew D, Kishore BN, Shwethadri GK, Sukumar, Shetty NJ. An evaluation of clinical and histological status in paucibacillary leprosy persists after fixed duration therapy. *Indian J Lepr* 2004; **76**: 8-11.
16. Britton WJ, Lockwood DNJ. *Leprosy Lancet* 2004; **363**: 1209-1219.
17. Norman G, Joseph G, Richard J. Relapses in MB patients treated until smear negativity: findings after 20 years. *Int J Lepr Other Mycobact Dis* 2004; **72**: 1-7.
18. Halder A, Mahapatra BS, Mundle M, Halder S, Sahu AK. A study of relapses after MDT in West Bengal India. *Indian J Lepr* 2003; **75**: 1-8.
19. Maeda S. Multi- drug resistant M. Leprae from patients with leprosy. *Nihon Honsenbyo Gakkui Zasshi* 2004; **73**: 227-33.
20. Deshmukh AR, Dhurat RS, Jerajani HR, Jerajani UR. A comparative clinico pathological study of single dose ROM in PB leprosy patients with 1-3 skin lesions. *Indian J Lepr* 2003; **75**: 209-17.
21. Villahermosa LG, Fajardo TT, Abalos RM, Cellona CV, Balagon MV, Dela Cruz EC, Tan EV, Walsh GP, Walsh DS. Parallel assessment of 24 monthly doses of rifampicin, ofloxacin, and minocycline versus 2 years of WHO multi drug therapy for MB leprosy. *Am J Trop Med Hyg.* 2004; **70**: 197-200.
22. World Health Organization. Report of the fourth meeting of the WHO technical advisory group on the elimination of leprosy. WHO/CDS/CPE/CEF/ 2002: 32.
23. Saunderson P. Uniform MDT (U-MDT) regimen for all leprosy patients - another example of wishful thinking. Editorial. *Lepr Rev* 2003; **74**: 2-6.
24. Kaotch K, Kaotch VM, Natarajan M, Gupta UD, Sharma VD, Shivanarar CT. 10-20 year follow up of highly bacillated BL/LL leprosy patients on combined chemotherapy and immunotherapy. *Vaccine* 2004; **22**: 3649-57.
25. Ragunathan RW, Atukorala DN, Gunawardena P. Leprosy - a study of reactions in Sri Lanka. *Sri Lanka Journal of Dermatology* 2005; **9**: 8-11.
26. Kumar B, Dogra, Kaur I. Epidemiological characteristics of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2004; **72**: 125-33.
27. Naafs B. Current views on reactions in leprosy. *Indian J Lepr* 2000; **72**: 97-122.
28. Campos NS, De Sousa PR. Reactional states in leprosy. *Int J Lepr* 1954; **22**: 259-67.
29. Lockwood DNJ, Vinayakumar S, Stanley JNA. Clinical features and outcome of reversal (type 1) reactions in Hyderabad, India. *Int J Lepr* 1993; **60**: 8-15.
30. Naafs B Treatment of reactions and nerve damage. *Int J Lepr* 1996; **64**: S21-S28.
31. Marlowe SN, Hawksworth RA, Butlin CR, Nicholls PG. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg.* 2004; **98**: 602-9.
32. Parikh AC, Ganapathi R, Kothare KB. Decompression of the ulnar and median nerves in leprosy neuritis. *Lepr Rev* 1968; **39**: 143-46.
33. Palande DD. A review of 23 operations on the ulnar nerve in leprosy neuritis. *J Bone Joint Surg* 1973; **55A**: 1457-64.
34. Schreuder PAM. Chronic recurrent ENL, steroid dependent: long term treatment with high dose Clofazimine. *Lepr Rev* 2003; **74**: 386-89.
35. Helmy HS, Pearson JM, Waters MF. The treatment of moderately severe erythema nodosum leprosum with clofazimine - a controlled study. *Lepr Rev* 1971; **42**: 167-77.
36. Imkamp FM. The treatment of corticosteroid dependent lepromatous patients in erythema nodosum leprosum with clofazimine. *Lepr Rev* 1973; **44**: 127-33.
37. Plock H, Leiker DL. A long term trial with clofazimine in reactive lepromatous leprosy. *Lepr Rev* 1976; **47**: 25-34.
38. de Carsalade GY, Achirafi A, Flaguel B. Pentoxifyline in the treatment of erythema nodosum leprosum: results of an open study. *Acta Leprol* 2003; **12**: 117-22.
39. Mahajan VK, Sharma NL, Sharma RC, Sharma A. Pulse dexamethasone, oral steroids and azathioprine in the management of erythema nodosum leprosum. *Lepr Rev* 2003; **74**: 171-4.
40. Sarojini PA, Mshana RN. Use of colchicines in the management of ENL. *Lepr Rev* 1983; **54**: 151-53.
41. Jakeman P, Smith WCS. Thalidomide in leprosy reaction. *Lancet* 1994; **343**: 432-3.
42. Crawford CL. Use of thalidomide in leprosy. *Adverse Drug React Toxicol Rev* 1994; **13**: 177-92.
43. Richardus JH, Nicholls PG, Croft RP, Withington SG, Smith WC. Incidence of acute nerve function impairment: a prospective cohort analysis after 5 years of follow up. *Int J Epidemiol* 2004; **33**: 337-43.
44. Smith WC, Anderson AM, Withington SG, van Brekel WH, Croft F, Nicholls PG, Richardus JH. Steroid prophylaxis for the prevention of nerve function impairment in randomized placebo controlled trial (TRIPOD 1). *BMJ* 2004; **328**: 1459-64.
45. Van Brekel WH, Anderson AM, Withington SG, Croft RP, Nicholls PG, Richardus JH, Smith WC. The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev* 2003; **74**: 300-10.
46. Richardus JH, Withington SG, Anderson Am, Croft RP, Nicholls PG, Van Brekel WH, Smith WC. Treatment with corticosteroids of long standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *LEP Rev* 2003; **74**: 311-18.
47. Cross H, Newcombe L. An intensive self care training programme reduces admissions for the treatment of planter ulcers. *Lepr Rev* 2001; **72**: 276-84.
48. A guide to leprosy control. WHO. Geneva. 1988.