Report of Informal Consultation on Treatment of Reactions and Prevention of Disabilities

11-13 December 2018, Chennai, India
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# Abbreviations and acronyms

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<th>Description</th>
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<tbody>
<tr>
<td>BI</td>
<td>bacillary index</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life year</td>
</tr>
<tr>
<td>ENL</td>
<td><em>erythema nodosum leprosum</em> (Type 2 Reaction)</td>
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<tr>
<td>G2D</td>
<td>grade-2 disability</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>MB</td>
<td>multi-bacillary</td>
</tr>
<tr>
<td>MDT</td>
<td>multidrug therapy</td>
</tr>
<tr>
<td>MFT</td>
<td>monofilament testing</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>NFA</td>
<td>nerve function assessment</td>
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<tr>
<td>NFI</td>
<td>nerve function impairment</td>
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<tr>
<td>NLEP</td>
<td>National Leprosy Eradication Programme (India)</td>
</tr>
<tr>
<td>NLP</td>
<td>national leprosy programme</td>
</tr>
<tr>
<td>PB</td>
<td>pauci-bacillary</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Reversal Reaction (Type 1 Reaction)</td>
</tr>
<tr>
<td>ST</td>
<td>sensory testing</td>
</tr>
<tr>
<td>TAG</td>
<td>WHO Technical Advisory Group on Leprosy</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TNFα</td>
<td>tumor necrosis factor-alpha</td>
</tr>
<tr>
<td>VMT</td>
<td>voluntary muscle testing</td>
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<td>WHO</td>
<td>World Health Organization</td>
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**Executive Summary**

Reactions are acute exacerbations of signs and symptoms of leprosy occurring during the natural history of the disease affecting skin, nerves, eyes or limbs. Left untreated or improperly managed, reactions can lead to nerve function impairment (NFI) and subsequently to disabilities. Reactions and neuritis remain an enigma for many frontline health staff treating leprosy. The problem is more noticeable in an integrated health care setting. Data collected from national leprosy programmes (NLPs) showed that in 2017, 7332 patients were treated for Type 1 Reaction (also known as Reversal Reaction or RR) and 5370 patients have been treated for Type 2 Reaction (also known as *erythema nodosum leprosum* or ENL).

Prevention of disabilities starts with early detection of reactions, prompt recognition of NFI and effective treatment of neuritis. These are the essential steps during the management of the disease for ensuring good quality and holistic treatment to persons affected by leprosy. The most recent World Health Organization (WHO) technical guidance on treatment of reactions and prevention of disabilities dates from 2010. Since then approaches to managing reactions have further improved. This informal consultation aimed to review the evidence on treatment practices followed for managing reactions in leprosy.

Reactions in leprosy are important clinical events (occurring before, during and even after completion of treatment) that may influence treatment or affect the quality of life. All patients with reactions and neurological events should be documented and properly managed. Patients with reactions should be monitored once in two weeks. Adverse events due to anti-leprotic drugs or drugs used to managed reactions and mortality associated with reactions need to be documented and reported.

Steroids (oral prednisolone) remains the main choice for treatment of RR. Frontline health workers need to be trained in recognizing RR and referring such patients for proper management. Likewise, ENL needs to be recognized and its severity measured. Patients need to be warned that this may constitute a chronic complication. They need treatment with steroids, but second-line drugs should be made available in order to reduce the morbidity and mortality associated with steroids. National programmes should develop recommendations for second line treatment of ENL. The use of thalidomide in the treatment of ENL should be reinstated as per the WHO Technical Report Series 968 of the WHO Expert Committee on Leprosy Eighth Report 2012.

Nerve function assessment (NFA) is required for the prevention of disabilities and should be introduced at all health facilities treating leprosy. A simple algorithm needs to be developed for use by frontline health workers to screen leprosy patients and identify those patients with higher risk for NFI.

Calculation of disability-adjusted life years (DALYs) in leprosy needs further understanding for finalizing a score considering disabilities, mortality due to reactions and discrimination against persons affected by leprosy.
1. Inaugural session

On behalf of WHO, Dr Isabelle Roger, Regional Adviser for Neglected Infectious Diseases and Leprosy, WHO Americas Region, extended a warm welcome to all participants. Participants included representatives of selected NLPs, local government staff, experts in the field of leprosy, members of the WHO Technical Advisory Group on leprosy (TAG) and WHO staff. She mentioned that treatment of reactions has become an important component in the management of leprosy and underscores the quality of treatment.

Dr Shaikh Noordeen, Director (retired) of the Department of Leprosy of WHO, referred to the dedicated leprosy work undertaken in Chennai and surrounding districts of India, reducing the prevalence rates from more than 100 to less than 0.5 per 10 000 over a period of five decades. He congratulated WHO for organizing this informal consultation on very important topics that are part of the management of leprosy such as treatment of reactions and prevention of disabilities. A clear guidance coming out of this consultation would benefit health workers in managing leprosy patients in the field with limited facilities available. He mentioned that it was time that more health professionals are co-opted and partnered with persons affected by leprosy to improve the reach of services and also to reduce the disease burden due to leprosy.

In her opening message, Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia Regional Singh appreciated significant milestones reached in leprosy control, including elimination as a health problem globally and in most countries. New cases, however, continue to occur: in 2017, data from more than 150 countries showed that 210 671 new leprosy cases were reported. More than 5% showed grade-2 disabilities (G2D) at the time of diagnosis. Among them, 238 children were notified. She underscored the importance of WHO’s Guidelines for the diagnosis, treatment and prevention of leprosy. She further emphasized the need for improving the quality of treatment and preventing disabilities and stigma associated with disabilities changing the way people think about and treat people suffering leprosy. The Regional Director also mentioned that reactions constitute acute conditions that trigger nerve involvement and may cause permanent physical disabilities. As NLP reviews highlighted the need for clarifications on the management of reactions by health professionals (and in particular frontline health workers), the experts were requested to deliberate on the available evidence and provide clear guidance on the subject.

Objectives and expected outcomes

The overall objective was to reduce the disease burden due to leprosy by improving the quality of care for patients on treatment.

The specific objectives of the informal consultation were:

- To discuss the current treatment practices in managing reactions: RR (or Type 1 Reaction), ENL (or Type 2 Reaction) and neuritis occurring in leprosy;
- To develop algorithms for screening of patients at diagnosis and during treatment of leprosy for preventing deformities in hands, feet and eyes;
- To identify updated approaches for managing reactions to recommend to countries.
The expected outcomes were:

✓ Technical guidance on the management of reactions in leprosy for NLPs;
✓ Algorithm for NFA to prevent disabilities at diagnosis, during and after treatment.

2. Current guidance on treatment of reactions and prevention of disabilities in leprosy

The current guidance on treatment of reactions mainly stems from the report of the Eighth meeting of the WHO Expert Committee on Leprosy, which was held in 2010. Nerve function impairment often results from various pathological and immunological processes in leprosy, often termed reactions. Leprosy reactions are considered leading causes of disability because reactions, if left untreated or improperly managed, may lead to irreversible damage causing physical deformities or G2D. Reactions appear to occur in a significant proportion of patients: up to 30% of patients diagnosed with multibacillary (MB) disease. Steroids remain the mainstay of treatment of reactions. For treatment of RR, steroids are advised for a period of 12 to 20 weeks starting with an initial dose of 40 mg of oral prednisolone to be administered as a single dose in the morning and gradually tapered by 5 mg every two weeks. For treatment of ENL, steroids are advised during the acute phase. For cases which show recurrence or chronicity, the treatment needs to be fortified with clofazimine, which has known anti-inflammatory action. At start 100 mg of clofazimine three times a day is prescribed; the dosage is subsequently tapered over a period of 36-48 weeks depending on the severity and chronicity of the reactions. Though many studies have demonstrated effectiveness of thalidomide in treating acute ENL, its use is restricted in many countries due to the teratogenic effects. WHO advocates that NLPs ensure an effective referral system and education of patients for seeking treatment on noticing signs and symptoms of reactions.

In both types of reactions general symptoms should be treated symptomatically. Patients should be screened for conditions where oral steroids are contra-indicated. Treatment of reactions should be supported with physiotherapy and counselling. Nerve function should be assessed frequently to prevent development of disabilities during the course of reactions. The technical guidance on reactions underlines the importance of early detection and institution of the correct treatment and required physiotherapy. It has been noted that reactions may occur before diagnosis, during and even after treatment with multidrug therapy (MDT). Patients on MDT are advised to continue MDT while reactions are managed.

3. Reversal Reaction or Type 1 Reaction

3.1. Literature review

Type 1 Reaction or RR is a major cause of NFI in leprosy and affects up to 30% of susceptible individuals. It occurs due to sudden alteration in cell-mediated immunity, a delayed type hypersensitivity. Type 1 reactions may be a presenting feature of leprosy or occur during treatment with multidrug therapy (MDT) or even after it has been completed. If the reaction is mild and there is no evidence of neuritis, analgesics such as acetylsalicylic acid or paracetamol are usually sufficient.
the presence of nerve involvement, analgesics and oral prednisolone is used at a dose of 40-60 mg daily which is gradually reduced weekly or fortnightly and stopped after 12 weeks.

Corticosteroids are the drugs of choice in the treatment of RR due to their inhibition of the pro-inflammatory cytokine milieu that aid in the recovery of NFI. Therefore, immunosuppressive doses of corticosteroids are required for prolonged periods, as the reaction will persist or recur even whilst the bacillary load gradually falls. Clinically, corticosteroids reduce intraneural and cutaneous edema, leading to quick improvement of symptoms, and they reduce post-inflammatory scarring. The existing reports provide conflicting data regarding adequate duration of steroid treatment in RR.

Review of the literature showed that 20 weeks of oral prednisolone is effective in controlling RR with recent NFI. Twelve weeks of prednisolone therapy for RR in borderline or borderline-lepromatous patients was found to be inadequate, with one-third of patients relapsing; extension of therapy to 20 weeks resulted in a low recurrence rate. The Cochrane systematic review of corticosteroids for treating nerve damage in leprosy identified only three randomized controlled trials (RCTs) that met the review criteria; it concluded that long-term steroids did not have significant effect on the outcome of nerve damage.

Second-line drugs used in the treatment of RR include azathioprine and cyclosporine. Cyclosporine could be a safe alternative for patients with RR who are not improving with prednisolone or are experiencing adverse events related to prednisolone and where azathioprine is not recommended.

Evidence from RCTs does not show a significant added benefit of surgery over steroid treatment alone. Relevance of prednisolone with respect to dosage and duration needs to be delineated. Scientific evidence on better regimens and/or alternate drugs (cyclosporine) should be considered for improving or standardizing RR treatment.

### 3.2. Clinical features of RR

Reversal reactions occur when the body’s immune response suddenly starts to become more active in attacking the leprosy bacilli in the body. The reason for this is not known in most cases, although the commonest time for RR to occur is during the first 3 to 6 months of treatment – perhaps the rapid killing of most bacilli gives the immune response a sudden boost. The next most frequent time for a RR to appear is actually before treatment has started and is a common way in which leprosy is diagnosed; a painless skin lesion may not cause a person to seek medical help, but if it suddenly becomes painful and swollen (as occurs during RR), they may seek treatment. The result is inflammation of the tissues where the bacilli are found, in particular the skin and the nerves (Lockwood, 1993).

Inflammation of the nerves can happen with RR and is covered more definitively in a different section. Inflammation that occurs with RR as a consequence of the immune response, produces changes in the tissues, leading to typical clinical features. The skin lesions become red and swollen; they become warmer and tender to touch; any nearby joints may be more difficult to move (loss of function). New skin lesions may appear. In a mild RR, although the skin lesion may be warm, the body temperature may remain normal; with a more severe RR the body temperature is likely to be raised.

In general, inflammation of the skin in RR is not a serious problem, as the reaction is self-limiting. Symptomatic treatment is required until resolution over a period of a few weeks. An important issue,
however, is that RR in the skin is very often accompanied by neuritis, which can have serious consequences, included permanent nerve damage, impairment and disability. A RR in the skin may therefore be taken as a possible pointer of impending neuritis (Nery, 2013). Special attention should be taken with reactional lesions located on the face, because they are associated with a high risk of facial nerve damage, resulting in lagophthalmos and its consequences (Hogeweg, 1991).

3.3. Diagnostic procedures, including laboratory tests

The diagnosis of RR is essentially clinical, with the finding of inflamed skin lesions. The presence of fever would indicate a more severe RR. There are two specific types of diagnostic procedure that are indicated in patients with RR: (i) tests of nerve function to identify any accompanying neuritis; and (ii) tests to look for any contra-indication to treatment with steroids.

Clinical tests include nerve function tests for both sensory and motor functions of the half dozen or so nerves most at-risk in leprosy. The methods are described under the section on neuritis.

The tests needed prior to starting a course of steroids are described below.
3.4. Recommended treatment regimens

Steroids (oral prednisolone) remains the main choice for treatment of RR. Frontline health workers need to be trained in recognizing RR and referring them for treatment. Steroids suppress the T-cell driven inflammatory response to *M. leprae* antigens within the skin and nerves. Therefore, immunosuppressive doses of corticosteroids are required for prolonged periods, as the reaction will persist or recur even whilst the bacillary load gradually falls (Kumar, 2009).

Aspirin is a safe anti-inflammatory drug and can be used to treat RR while the patient is waiting for an expert assessment. Once a definitive diagnosis is made, however, a steroid course is recommended in order to manage any neuritis that may be developing (Girdhar, 2007). The best steroid regimen to treat reactions and neuritis continues to be debated, both in terms of dose and duration. One trial suggested that a 20-week course gave better results than a 12-week course, but that higher starting
doses were not more effective (Rao, 2006). A subsequent trial – known as “TENLEP” – showed that prolonging the course to 32 weeks provided little additional benefit (Wagenaar, 2017).

The recommended course of steroids therefore lasts for 20 weeks, as follows (Rao, 2006):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>30 mg / day</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>25 mg / day</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>20 mg / day</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>10 mg / day</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>5 mg / day</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20 weeks</td>
</tr>
</tbody>
</table>

In the TENLEP study, the 20-week regimen started with a higher dose (1 mg / kg, up to 60 mg) for one week but was in other respects very similar, with an 8-week period in the middle at 20 mg daily (Wagenaar, 2017). It is important to note that around 15% of patients in both groups of this trial (i.e. 20 and 32 weeks treatment) required extra prednisolone because of a lack of improvement or worsening once the standard course ended. The reactions were eventually well controlled with this additional treatment.

Steroids have a number of adverse effects. Two in particular need to be monitored, often with laboratory tests:

1. Steroids depress the immune system so may allow certain dormant infections to flourish. The most important of these is tuberculosis (TB), but it takes time for it to cause symptoms, so the link may not be realized; however, it is important to ask about any symptoms suggestive of TB, and do the appropriate tests, if indicated. Certain gut infections, in particular strongyloidiasis, can cause severe disease; because of the difficulty in diagnosing the quiescent state, it is recommended to give single dose albendazole to anyone starting steroids.

2. Steroids may also precipitate diabetes in some patients (particularly if high doses are given to patients who are overweight) or worsen it in those already with it. Glucose tolerance tests are, therefore, useful (including urine sugar and random blood sugar as the most basic). A blood sugar level done two hours after a glucose drink is also a useful screening test.

3.5. Counseling of patients

All patients should receive counseling when a diagnosis of leprosy is made, when needed during the course of treatment and also when they are released from MDT treatment. This will inform them of the possibility of reactions, in which the symptoms of the disease appear to worsen. They should be aware of the need to continue normal treatment, while seeking additional help for the new symptoms. Most reactions subside over a period of weeks or months, but they sometimes recur and become more chronic. Treatment of reactions is not easy as the drugs have significant side effects but the symptoms can usually be well-controlled.
3.6. Follow-up and treatment monitoring

It is important to record:

✓ All episodes of reactions, including clinical features (skin lesions and nerve involvement), severity and duration;
✓ Details of any nerve function assessments; and
✓ Details of treatment given, in particular the dosage and duration of steroid treatment.

Anyone on treatment with steroids should be seen at least every two weeks. Once steroids have been stopped the patient should be seen every month initially, then every three months, to monitor nerve function.

3.7. Further research

The following areas of research were proposed:

▪ Drugs or vaccines that may minimize the interaction of the leprosy bacillus with the nerves, thus reducing nerve involvement and nerve damage, which occurs during reactions;
▪ Role of viable or persistent M. leprae in predicting RR;
▪ Alternatives to steroids in the treatment of RR;
▪ Methods to help patients become more aware of reactions and thus seek treatment early.

3.8. References

4. Erythema Nodosum Leprosum or Type 2 Reaction

4.1. Working group for ENL

A working group with the following members was constituted to support the consultation process and bring out recommendations on ENL:

- Professor Diana Lockwood, London School of Hygiene and Tropical Medicine, Facilitator;
- Dr V V Pai, Director, Bombay Leprosy Project, Mumbai, India;
- Dr Mahesh Puri, National Leprosy Programme, Kathmandu, Nepal;
- Dr Joydeepa Dalrong, Lead presenter on ENL, The Leprosy Mission Trust India.

The working group was assigned responsibility of carrying out literature review, compiling and presenting key findings and recommendations from the literature review, facilitating group work and prepare a technical guidance document drawing from the discussions, literature review and inputs provided by the participants in the workshop.

4.2. Current status

Erythema nodosum leprosum is a multisystem, relapsing and remitting disorder occurring in patients with lepromatous and borderline lepromatous leprosy. The incidence varies in different cohorts, from 5% (Saunderson et al., 2000) to 40% (Pocaterra et al., 2006). The incidence also varied between countries: 5% in Ethiopia; 19%-26% in India, Nepal and Thailand; and 37% in Brazil. Risk factors include lepromatous leprosy or a bacillary index over 4.3.

The natural course of ENL is between one and two weeks, but many patients experience multiple recurrences for months (Scollard et al., 2006). Type 2 Reaction is, hence, classified as mild, moderate and severe. The review of current treatment practices of ENL reaction has become necessary because of the following reasons: (i) mechanisms leading to ENL are not fully understood, which makes treatment difficult; (ii) corticosteroids, clofazimine and thalidomide are the drugs of choice for treatment of ENL; (iii) all treatment options have drawbacks and the optimal regimen is yet to be established; (iv) alternative therapies have been tested but it is unclear if they are beneficial or which one is preferable; (v) the role of newer treatments such as tumor necrosis factor-alpha (TNFα) antibody treatment, intravenous immunoglobulin or tenidap is not known.

INFOLEP and PUBMED were systematically reviewed for articles based on cohort, case–control, cross-sectional and ecological studies. Treatment of mild ENL is usually done with anti-inflammatory drugs, such as acetylsalicylic acid, indomethacin, paracetamol at a dose of 1000 mg every eight hour. Corticosteroids are suggested for recurrent ENL, which results in rapid and defined therapeutic action (Mahajan, 2003 and Van Veen, 2009). Recurrent ENL sometimes requires prolonged dose of steroids (Darlong et al). Prolonged use of steroids might cause dependence (Lockwood, 1996). Prolonged use
of steroids is also associated with serious side effects and needs constant supervision by medical professionals particularly when patients are treated with high doses (Sugumaran, 1998).

Clofazimine is advised for the treatment of chronic ENL. The dose used in the treatment of ENL is higher than the one used in MDT. Clofazimine takes 4-6 weeks to become effective and does not have action on acute attacks. It is mainly effective on preventing repeated attacks and reducing steroid dependence. Skin pigmentation is one of the adverse effects associated with clofazimine. Thalidomide is another drug with proven effect in reducing the severity of acute attacks and recurrence of ENL. The drug is not available in many countries as it is associated with serious adverse events, teratogenicity, sedation, peripheral neuropathy (Calabrese and Fleischer, 2000; Wines et al., 2002) and thromboembolic complications (<5% risk; Wu et al., 2005). Revlimid® (lenalidomide) and akthimid (lenalidomide) are analogous drugs which have shown promising results and reduced side effects (Kaplan et al.). Other drugs include pentoxyfylline (slow acting drug, needing 30-60 days), azathioprine (reduces frequency of ENL), methotrexate (useful in patients with resistant ENL) and cyclosporine (more effective in acute attacks).

Lack of clear-cut information on early predictors of reaction, deciding minimal effective dose of steroids, management of unresponsive, resistant ENL, early detection of steroid dependence among patients, robust monitoring of steroids and thalidomide are a few areas where more research is needed.

There have been a number of publications on ENL since last guidelines written including systematic reviews and trials (thalidomide, cyclosporin, methotrexate). Epidemiological studies have shown that ENL is a significant problem. Studies were also carried out on ENL chronicity and morbidity, related to prolonged steroid use, and mortality. Patients with ENL have Impaired quality of life and catastrophic household economic costs.

The ENLIST consortium (global consortium to improve understanding and treatment of ENL with representatives from Bangladesh, Brazil, Ethiopia, India, Indonesia, Nepal, and the Philippines) has contributed to developing work on ENL.

### 4.3. Detection and classification of ENL

Patients at risk of ENL typically have a bacillary index (BI) <4. ENL can occur during or after MDT. This is a further argument for continuing to provide slit skin smear services at referral centres so that at-risk patients can be identified. Recording of rates of ENL by national programmes is generally poor.

The clinical features of ENL are:

<table>
<thead>
<tr>
<th>System affected</th>
<th>ENL features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>red, tender/painful subcutaneous nodules, any parts of the body</td>
</tr>
<tr>
<td>General symptoms</td>
<td>fever, malaise, pain</td>
</tr>
<tr>
<td>Other organs</td>
<td>joints/bones, eyes, testes, kidney</td>
</tr>
<tr>
<td>Nerves</td>
<td>peripheral nerves affected but not as common as in RR</td>
</tr>
</tbody>
</table>
ENL is diagnosed clinically when patients have some of the above features. The ENLIST severity scale is recommended to assess the severity of ENL. This has been validated prospectively. A score of <8 occurs in mild ENL while scores of >8 are associated with severe ENL.

Laboratory investigations for ENL are not needed to confirm the diagnosis but are needed to monitor the complications that may occur as a result of the immunosuppressant drugs that are given (blood sugar, complete blood count). Stool examination for parasites, HIV test, TB screening (symptom screening and sputum culture) when indicated. At the referral level erythrocyte sedimentation rate, renal function, hepatic function, eyes check and bone density monitoring should be done.

Three types of ENL have been described:

- **Acute**: episode of ENL lasting less than 6 months in which treatment was slowly withdrawn with no recurrence of ENL whilst on treatment;
- **Recurrent**: at least one further episode of ENL occurring 28 days or more after withdrawal of treatment for ENL;
- **Chronic**: episode of ENL lasting longer than 6 months during which patient is on continuous ENL treatment or any treatment free periods are less than 28 days.

### 4.4. Treatment of ENL

Treatment depends on the severity of the episode and needs to control the inflammation and pain.

#### 4.4.1. Mild ENL

Mild ENL is managed with analgesics (aspirin, indomethacin, ibuprofen, diclofenac, acetaminophen, tramadol). If there is worsening and increase in the score to >8, ENL should be reclassified as “severe” and managed accordingly. Monitoring should be done every two weeks.

#### 4.4.2. Moderate ENL

Steroid treatment is used starting with moderate doses of 30-40 mg prednisolone per day. They have a rapid and defined therapeutic action (Mahajan et al., 2003; Van Veen et al., 2009). Recurrent ENL requires increased or prolonged doses of steroids to control the inflammation and symptoms. Patients with chronic ENL may become dependent on steroids. Serious side effects of long steroid treatment course have been reported. Walker et al. found a 9% mortality in Ethiopian patients taking steroid treatment for ENL; this was caused by steroid-related complications such as sepsis and occurred mostly in young people.

Steroid doses may need to be increased if ENL severity increases up to 40-60 mg prednisolone per day depending on body weight. The treatment duration is 20 weeks. The dose of prednisolone should be reduced as follows:
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>40 mg / day</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>30 mg / day</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>20 mg / day</td>
<td>4 weeks</td>
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<td></td>
<td>15 mg / day</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>10 mg / day</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>5 mg / day</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>20 weeks</strong></td>
</tr>
</tbody>
</table>

Gastric protection can be given with a proton pump inhibitor e.g. omeprazole. Calcium and Vitamin D supplements should be given as well as anti-helminths (e.g. albendazole). If the patient is on MDT this should be continued until the treatment course is completed. Comorbidities should be treated appropriately.

Co-morbidities can be detected by asking about history and symptoms. Diabetes, hypertension, coronary vascular disease, dyslipidemia, peptic ulcer, affective disorders, fractures, ongoing infections, acne, fungal infections, TB, concomitant medications; traditional medicines or self-administered after consulting the internet.

Physical examination should include: weight, height, body mass index, blood pressure, signs of sepsis. History should include diabetes, symptoms of peptic ulcer, abdominal surgery. Any ulcers or infections (if patient has ulcer or infection and needs steroids, admit, treat and give under supervision. But consider deferring steroids till the crisis is over).

Investigations to be undertaken include: urine analysis, haemoglobin, complete blood count, erythrocyte sedimentation rate, lipid profile, HIV, chest X-ray (if clinical suspicion of TB), blood sugar, stool examination for ova and cysts for protozoal and parasite worms.

The Indications for using thalidomide or other second-line drugs are:

✓ Steroid non-responder: those requiring higher doses of steroids with each episode of ENL;
✓ Steroid dependent: those for whom tapering the steroid results in flares; and
✓ patients with a serious comorbidity

Patients can develop hypo-adrenalism (Addisons’s Disease) secondary to the prolonged courses of steroids. This can be screened for by monitoring blood pressure and electrolytes. A detection and management protocol should be developed for this complication as it is probably under-recognised.

Thalidomide is an effective alternative, giving rapid symptom control. Kaur et al. showed that thalidomide gave better symptom control than prednisolone. Nabarro et al. showed that using thalidomide reduced dependence on prednisolone. There are recognized adverse events with thalidomide including sedation, peripheral neuropathy. Thromboembolic complications carry a <5% risk. Teratogenicity when taken early in pregnancy is a major complication of thalidomide. Women can be given thalidomide but only when being supervised in a prevention of pregnancy programme. This includes patients being seen every 28 days, having negative pregnancy tests, before receiving a prescription for thalidomide.
WHO advice on the use of thalidomide

The advice from 2012 states correctly that “Several studies demonstrated usefulness of thalidomide. Its use should be restricted due to its teratogenic effects and restricted availability in countries. Administration is recommended under strict medical supervision in referral hospitals”. http://www.searo.who.int/entity/global_leprosy_programme/documents/WHO_expert_comm_8th_report/en/.

However, an earlier report from another web link goes to a document titled “No Role for Thalidomide in Leprosy” (https://www.paho.org/hq/dmdocuments/2013/No-Role-Thalidomide-Leprosy-2003-Eng.pdf).

Clofazimine is widely used in Management of ENL. However, there is no good data showing that it is effective. It takes 4 to 6 weeks to become effective. The dose required to control ENL is higher than the dose used in MDT (van Veen et al., 2009). It has no effect on acute episodes but might be effective on chronic ENL. The associated skin pigmentation may be stigmatizing (van Veen et al., 2009). A recent study in the Philippines, in which patients were randomized to receive clofazimine 100 mg per day or placebo, showed no benefit for clofazimine in reducing ENL frequency or severity.

Other drugs have been used as second-line treatments for ENL. they have all been used in small-scale studies. They are: pentoxifylline, methotrexate, cyclosporine and azathioprine. The effectiveness of methotrexate will be tested in a large RCT expected to start in mid-2019.

TNFα inhibitors (e.g. infliximab in one case and etanercept in three cases) have been used to treat patients with recurrent ENL. This is an area that will see expansion over the next few years as biological agents become cheaper and more widely used. It is important that more clarity is provided on the use of biological agents in management of ENL.

4.5. Patient counselling

Patients should be warned that ENL may last for over a year. They should be counselled about controlling their symptoms. They should be given a steroid information leaflet and a steroid card. They should be warned against buying over-the-counter steroids to treat their symptoms. It is important that they are monitored by a clinician experienced in managing patients with ENL. They may develop depression about their condition and the medication they are taking. This should also be asked about in clinic visits. National leprosy programmes should provide information leaflets for patients about ENL and its treatment.

4.6. Recommendations and further research

➢ The recommendations by WHO on the treatment of ENL should be evidence-based and done through a systematic review.

➢ Using thalidomide as a second-line drug in Africa where there is currently very little use will save lives, because patients with ENL in Africa are dying from steroid-related complications.
➢ WHO should align advice on thalidomide and ensure that the advice to use thalidomide is consistent.

➢ Research should be done on the effectiveness of thalidomide in new trials. These could be done in Africa and Indonesia. This would promote the use of thalidomide and help develop clinical research in Africa.

➢ National leprosy programmes should have ENL detection and management plans with patient information leaflets.

➢ Research should be done on understanding the pathogenesis of ENL. It probably involves several different pathologies.

➢ Research should be done to determine whether there is a genetic susceptibility to ENL.

4.7. References


5. Neuritis

5.1. Working group for neuritis

A working group with the following members was constituted to support the consultation process and draft recommendations on neuritis:

- Professor Mohan D Gupte, Chair, TAG; Facilitator
- Dr Roch Christian Johnson, President, International Leprosy Association;
- Dr Vanaja Shetty, Director, Foundation for Medical Research, Mumbai, India; and
Dr Saba Lambert, ALERT Ethiopia; Lead presenter on neuritis

The working group was assigned responsibility of carrying out literature review, compiling and presenting key findings and recommendations from the literature review, facilitating group work and prepare a technical guidance document drawing from the discussions, literature review and inputs provided by the participants in the workshop.

5.2. Current situation

Neuritis describes inflammation in a nerve. Symptoms may include: pain, paraesthesia (*pins-and-needles*), paresis (weakness), hypoesthesia (numbness), anaesthesia, paralysis, wasting and disappearance of the reflexes. *M. leprae* causes gradual nerve damage by wallerian degeneration and demyelination. Additional nerve damage occurs when further inflammation or neuritis occurs. Nerve damage is described in different forms such as acute neuritis, peripheral neuropathy, pure neural leprosy (4-8% of leprosy cases). Silent neuritis, autonomic neuritis, cranial nerve involvement, and neuropathic pain. Acute neuritis occurs during leprosy reactions. In a large (*n* = 1972) clinical study, 6.9% of patients had neuritis without other signs of reactions (Scollard, 2015). Change in the immunological status of the patients before starting treatment, during treatment and after completion of treatment result in worsening neurological manifestations. Neuritis occurs more commonly with RR. Neuritis occurs in up to 30% of MB cases.

Edema and painful infiltration of CD4-positive lymphocytes into skin caused by increased T-cell reactivity to mycobacterial antigen associated with infiltration of interferon-gamma and TNFα and associated with increased serum cytokine concentration (Manandhar, 2002). Cytokine levels decrease with corticosteroids and a poor response do corticosteroids mean persistently high cytokine levels and an increases likelihood of a relapse of neuritis after steroid withdrawal.

Acute neuritis starts with spontaneous nerve pain, paraesthesia and nerve tenderness. If not contained or reversed, it may lead to NFI, with objective sensory-motor loss. Recognition of symptoms at onset and initiation of steroids reduce long-term nerve damage (Walker and van Brakel, 2000).

The Bangladesh Acute Nerve Damage Study (BANDS) gave details of risk of developing NFI. Patients with PB leprosy and no nerve function loss had a 1.3% risk of developing NFI within the first two years after registration. The Nerve Function Impairment and Reactions (INFIR) cohort study concluded that patients with skin lesions overlying peripheral nerve trunks should be carefully monitored for development of sensory or motor impairment. The ALERT MDT Field Evaluation Study (AMFES) of 594 patients (300 MB and 294 PB) over 10 years observed that the risk factors for developing chronic or recurrent neuropathy include older age, delay in diagnosis, thickened nerves at diagnosis and occurrence of reversal and ENL reactions. Nerve conduction studies have demonstrated to be more sensitive in the detection of neuropathy compared to clinical examination (Hussain, 2007; Kar, 2013). Superficially located peripheral nerves can be evaluated in greater detail for thickening, nerve oedema, micro abscesses and alteration of fascicular architecture. High resolution imaging can be a good follow-up tool to assess the morphological changes with treatment.

Recognising neuritis early (both acute and quiet nerve paralysis), anti-inflammatory therapy including steroids, splinting/rest during active phase, monitoring the patient’s condition during treatment for
neuritis, supportive physiotherapy care and surgery in select cases constitute main components of management of neuritis. Though most patients respond to 12-20 weeks of prednisolone, different regimens are being advocated: WHO (12 weeks); ILEP (12 weeks for pauci-bacillary (PB) and 24 weeks for MB cases) and the National Leprosy Eradication Programme (NLEP) of India (20 weeks for all cases). It was observed in TENLEP that 15% of the patients need additional steroids.

5.3. Clinical features and diagnosis

Symptoms of neuritis may include: pain in the nerve, paraesthesia (*pins-and-needles*), paresis (weakness), hypoesthesia (numbness), anaesthesia, paralysis, wasting, and disappearance of the reflexes. Patients with skin lesions overlying peripheral nerve trunks should be carefully monitored for development of sensory or motor impairment.

A history of spontaneous nerve pain, paraesthesia, and nerve tenderness, followed by NFI is an important indicator. Clinically, nerve palpation for tenderness and nerve swelling should be followed by sensory testing with monofilaments and voluntary motor testing to assess degree of NFI and record the baseline.

Investigations that could be useful but not essential are nerve conduction study, nerve ultrasound, and nerve biopsy. Further research is required to assess how these investigations can be used to monitor the prognosis while managing neuritis.

Patients should be screened for other co-morbidities that are likely to impact treatment and management of NFI as well as screening for steroid side effects.

5.4. Management of neuritis

Neuritis should be managed properly:

- Early recognition of neuritis (acute /quiet nerve paralysis);
- Anti-inflammatory therapy including steroids;
- Splinting / rest during active phase;
- Monitoring;
- Supportive therapy, physiotherapy during recovery phase;
- Surgery in select cases: decompression or neurolysis.

Steroids, usually prednisolone, will be given in a similar regimen as for Type 1 Reaction: start steroids at 1 mg per kg per day, then taper over a period of 20 weeks.

If worsening NFI (defined as a decrease in sensory function by 3 points and motor function by 2 points between two visits while on steroids) is detected during the monthly review visits, then the advice is to hike steroids to 1 mg per kg. This should only be done twice at the very most, and nerve decompression should be considered in appropriate cases.
5.5. Counselling

All leprosy patients should be counselled about the signs of symptoms of neuritis to encourage early detection and treatment. It is known that nerves will respond much better to steroid therapy if treatment is initiated within 6 months of symptom onset.

Patients should also be counselled about the benefits and side effect of treatment and the importance of self-care activities to prevent worsening of any disability present.

5.6. Follow up of patients and monitoring results of treatment

Serial voluntary muscle test (VMT) and sensory test (ST) results should be recorded in the patient’s clinical records to ensure careful monitoring of progress.

Nerve function assessment is crucial in detecting neuritis. For new patients without nerve involvement, NFA should be done at least at diagnosis, every three months and at release from MDT treatment.

When patients present with reactions, NFA should be done at diagnosis, at the end of 2 weeks of starting treatment, and at least monthly.

Nerve function assessments should additionally be done each time a patient complains of a new decrease of sensation or motor function.

5.7. Neuropathic pain

Treated leprosy patients may experience tingling or burning pains in treated skin lesions and their hands and feet. These may be misdiagnosed as reactions. In the absence of nerve tenderness and new NFI the diagnosis of neuropathic pain should be considered.

Patients should be treated with an analgesic ladder starting with paracetamol, then using a non-steroidal such as ibuprofen. Many patients will need treatment with the antidepressant amitriptyline. Gabapentin can also be used for patients with pain that is not alleviated by other measures. Steroids are not recommended for neuropathic pain in leprosy.

5.8. Further research

- Nerve damage in leprosy as the result of infection + inflammation + other physical factors;
- Best way to monitor for neuritis? What amount of NFI is significant?
- Best treatment of neuritis to prevent disability?
- Is six months a reasonable cut-off? Should it be shorter?
- Research on chronic pain in leprosy: new aspects to be considered
- Quiet nerve paralysis in the context of MDT
5.9. References for neuritis in leprosy


6. Nerve function assessment

6.1. Working group for NFA

A working group with the following members was constituted to support the consultation process and draft recommendations on neuritis:

- Dr Carlos Wiens, member of WHO TAG, Facilitator;
- Dr Jerry Joshua, Director, Schieffelin Institute for Health Research and Leprosy Centre, Karigiri, India;
- Dr Linda Lehman, Senior advisor for morbidity management and disability prevention, American Leprosy Missions;
- Dr Kingsley Stanley, ALERT India, Lead Presenter on NFA.

The working group was assigned responsibility of carrying out literature review, compiling and presenting key findings and recommendations from the literature review, facilitating group work and prepare a technical guidance document drawing from the discussions, literature review and inputs provided by the participants in the workshop.

6.2. Current situation on NFA

NFI is defined as clinically detectable impairment of nerve functions that necessitate intervention. The level (severity) of NFI that is clinically detectable depends on the tool (sensitive) or method (grades or scales) of the test used. When NFI is not treated within six months of onset, nerve damage can become irreversible and can cause permanent disability. Therefore, periodic NFA is an essential
part of leprosy management. Nerve function impairment is associated with Type 1 Reaction as per evidence from different studies. The incidence rate of NFI with Type 1 Reaction ranges from 8.9% (Hyderabad study) to 36% (Malawi study).

The purpose of NFA is:

➢ To diagnose leprosy (one of the three cardinal signs) and to classify for treatment with MDT (two or more trunk (not cutaneous) nerves affected is classified as MB);

➢ To establish occurrence of NFI in an individual patient during or after MDT and decide on appropriate interventions to prevent neuropathy;

➢ To monitor the changes in nerve functions (recovery / deterioration) following therapy (primary outcome measure);

➢ To devoid the persons affected from being subjected to social identity of leprosy thereby reducing stigma and discrimination.

For carrying out NFA, health staff require reliable, affordable and easy-to-use tools along with standard screening methods to detect early neuropathy in field settings. The tools should be sensitive enough (i.e. low number of false-negatives) to correctly diagnose NFI but also specific enough (i.e. low number of false-positives) in order not to over-diagnose NFI. Studies indicate that skills and experience levels of healthcare personnel affect the reliability of testing. Established methods for NFA are nerve palpation, ST and VMT. The ballpoint pen (easily available) or nylon monofilament is commonly used for ST. For VMT, three grades (as suggested by J Watson) or the modified Medical Research Council (MRC) scale (0–5) is used.

Before NFI is clinically detectable, the majority of nerves already show some subclinical neuropathy that can be detected with more sensitive methods. The warm detection threshold and nerve conduction studies were able to detect subclinical neuropathy up to 12 weeks before the clinical neuropathy was noticeable with mono-filament testing (MFT) or VMT. Significant correlation was observed between clinical parameters – nerve thickening (palpation), sensory loss (MFT) and muscle weakness (VMT) – and abnormalities of nerve echotexture (ultrasound), endoneural flow and cross-sectional area (CD Imaging) (p ≤ 0.001). Nerve damage was sonographically more extensive and was observed even in nerves that are considered clinically normal (Jain S et al.).

Evidence suggests that MFT is more reliable than ballpoint pen testing. Substantial levels of under-diagnosis of sensory loss with ballpoint pen testing were observed (Koelewijn LF et al., 2003).

Nerve function should be assessed whenever the patient complains about pain, numbness or weakness and routinely every six months to detect early nerve function loss (Brandsma JW, 1981). Nerve function needs to be assessed at diagnosis (baseline) and repeated every month during MDT and upon completion of treatment (endline), thus 7 times for PB patients and 13 times for MB patients). J. Jiang et al. (1998) suggest that NFA should be done once in three months; when NFI is detected, it should be done monthly during steroid therapy and every three months after steroid therapy.

The patient needs to be involved by imparting proper counselling about neuropathy and its consequences explaining the importance of NFA and detecting symptoms of neuropathy.
6.3. Rationale for NFA

Nerve function assessment is an assessment activity that is a fundamental part of leprosy care. It is needed to identify and manage NFI at the time of diagnosis, during treatment and even after release from treatment. Nerve inflammation and damage can happen at any time (before, during and after treatment), especially when there are lepra reactions.

The assessment indicates if the sensory and motor function of nerves supplying the eyes, hands and feet are normal or if there is a change in or loss of function. It helps in deciding on appropriate interventions.

Early identification of nerve function change or loss enables earlier action to treat NFI, which can prevent (further) nerve damage and/or minimize disability.

As NFI often occurs insidiously, both health workers and persons affected may not be aware that nerve function is deteriorating unless an assessment is carried out.

It is useful to monitor the changes in nerve functions (recovery / deterioration) during treatment with steroid therapy (primary outcome measure).

Periodicity of NFA:

<table>
<thead>
<tr>
<th>Patient category</th>
<th>When to do NFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Start of MDT</td>
</tr>
<tr>
<td></td>
<td>Completion of MDT</td>
</tr>
<tr>
<td></td>
<td>Any time when there are complaints suggesting neuritis</td>
</tr>
<tr>
<td>Patients at higher risk of developing NFI</td>
<td>Every three months while on MDT</td>
</tr>
<tr>
<td></td>
<td>Every three months (until one year) upon completion of MDT</td>
</tr>
<tr>
<td></td>
<td>Thus 9 times during 24 months after diagnosis</td>
</tr>
<tr>
<td>Patients with NFI of less than six months and thus eligible for treatment with steroids</td>
<td>After two weeks after starting steroids</td>
</tr>
<tr>
<td></td>
<td>Monthly until completion of steroid course</td>
</tr>
</tbody>
</table>

A patient is considered at higher for developing NFI if:

- There are more than six skin lesions with or without nerve involvement (i.e. only enlarged nerve without existing NFI);
- There is a skin patch on the face or near the eye or in the areas supplied by a palpable or visibly enlarged trunk nerve without existing NFI;
- There is evidence of lepra reactions (Type 1 or 2) including acute neuritis, either new or treated in past six months without existing NFI;
- The slit skin smear is positive;
- The patient is classified as having MB leprosy.
6.4. Performing NFA

➢ Where should NFA be performed?

NFA should be performed:
- At any health unit treating patients with leprosy;
- During community sensitization and screening campaigns;
- At home (self-examination by persons affected by leprosy).

➢ Who should perform NFA?

NFA should be performed by:
- Any trained health worker;
- Any trained person affected by leprosy.

➢ How should NFA be undertaken?

The “LOFT” principle should be followed:
- **Listen** to patient complaints of pain, sensory loss, weakness or difficulties doing activities of daily living;
- **Observe** (i) eye for brightness of cornea, spontaneous blink and complete closure of the eyelid; and (ii) hands and feet for injuries, wounds and weakness in straightening fingers and toes, lifting feet;
- **Feel** for dryness, localized warmth on hands and feet and palpate nerves for pain and/or enlargement;
- **Test** (i) sensation (using graded Semmes-Weinstein monofilaments, if available), temperature, light touch (using ball point pen); (ii) strength of movement of eyes, hands and feet.

➢ Tools to be used for NFA

<table>
<thead>
<tr>
<th></th>
<th>Primary care centre</th>
<th>Referral centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
<td>Palpation</td>
<td>Palpation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Sensory function</td>
<td>Temperature: cotton swab with acetone (cold); hot/cold test-tubes</td>
<td>Quantitative pain thresholds and temperature (QST)</td>
</tr>
<tr>
<td></td>
<td>Touch: 2G monofilaments</td>
<td>Semmes-Weinstein monofilament kit</td>
</tr>
<tr>
<td></td>
<td>Touch pressure: 10G monofilaments</td>
<td>(0.05G, 0.2G, 2.0G, 4.0G, 10.0G and 300G)</td>
</tr>
<tr>
<td>Motor function</td>
<td>VMT: strong / weak / paralyzed</td>
<td>MRC Scale 0-5</td>
</tr>
</tbody>
</table>

6.5. Recording of NFA findings

A summary table of a simplified assessment of vision and NFA is shown below.
## Simplified vision and nerve assessment examination (1/2019)

<table>
<thead>
<tr>
<th>Name:</th>
<th>Age:</th>
<th>Occupation:</th>
<th>Date (1)</th>
<th>Date (2)</th>
<th>Date (3)</th>
</tr>
</thead>
<tbody>
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</table>

### Vision & Neurological Exam

#### Date (1) Date (2) Date (3)

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<tr>
<th>Right</th>
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#### EYES

<table>
<thead>
<tr>
<th>Vision &amp; Neurological Exam</th>
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<tbody>
<tr>
<td>Date (1)</td>
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<tr>
<td>Date (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date (3)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Visual acuity

- Cornea loss of sensation
- Blink decreased or Decreased sensation with 5 cm dental floss

#### Loss of muscle strength

- Eye closure
  - P = Paralyzed, W = Weak, S = Strong
- Lid gap: Light closure of eyes
  - Measure lid gap in mm
- Lid gap: Tight closure of eyes
  - Measure lid gap in mm

#### Nerve palpation

- Ulnar
  - P = Painful, E = Enlarged, N = Normal
- Peroneal
  - P = Painful, E = Enlarged, N = Normal
- Tibial
  - P = Painful, E = Enlarged, N = Normal

#### Evaluate loss of muscle strength in hands:

- Little finger out (abduction)
- Thumb up (abduction)
- Wrist up (extension)

#### Protective sensory loss to palm of hands

- Light touch with ballpoint pen or 4G monofilament
  - X = Loss of sensation
  - ✔ = Feels touch

#### Evaluate loss of muscle strength of feet:

- Foot up (dorsiflexion)
- Large toe up (extension)

#### Sensory loss to sole of feet

- Light touch with Ballpoint Pen or 10g monofilament
  - X = Loss of sensation
  - ✔ = Feels touch

#### Visible Impairments of the eyes

- Yes No Yes No Yes No

#### Visible Impairments of the hands

- Yes No Yes No Yes No

#### Wounds on hands

- Yes No Yes No Yes No

#### Visible Impairments of the feet

- Yes No Yes No Yes No

#### Wounds on soles of feet

- Yes No Yes No Yes No

#### WHO Disability Grade (0, 1, 2)

- EHF Score (0-12)
6.6. Algorithms for NFA

6.6.1. Algorithm 1

START
All leprosy patients at entry level
Perform NFA

Is neuropathy present?

NO
With impairment?

NO
Classify as "Low risk"

YES
Classify as "High risk"

Perform another NFA at end of MDT or as needed

Impairment at 6 months?

YES
Perform NFA: every 3 months, on completion of MDT, as needed within 1 year post-MDT, at 1 year after NFT

END

NO

Is neuropathy present?

YES
Start WHO recommended prednisolone regimen

Neurologic, clinical and dermatological evaluation after 2 weeks

Patient improved or did not worsen?

YES

NO
Re-evaluate (neurologic, clinical, dermatological) every month until end of prednisolone treatment

Refer for further evaluation and intervention

END
6.6.2. Algorithm 2

6.7. References


17. Balagon M, Saunderson PR, Gelber RH (2011) Does clofazimine prevent erythema nodosum leprosum (ENL) in leprosy? A retrospective study, comparing the experience of multibacillary patients receiving either 12 or 24 months WHO-MDT. *Lep Rev.* 82: 213–221


28. Hossain D. Using methotrexate to treat patients with ENL unresponsive to steroids and clofazimine: a report on 9 patients.


7. **Field visit**

Field visits were undertaken to observe patient services and treatment practices followed by the National Leprosy Eradication Programme of India. Padi Round Building urban primary health centre, Ambattur zone and Silver Jubilee leprosy and skin clinic, Saidapet Government hospital were the two field sites identified for field visits. The participants made presentation on their observations from the visits. The visits were facilitated by National Institute of Epidemiology, Chennai (a WHO collaborating centre).

➢ **Observations**

The visitors appreciated the quality of patient services observed in Tamil Nadu health facilities visited. They made the following observations:

- MDT was available in adequate quantities in both health facilities. Assessment, monitoring of nerve function at primary care was observed.
- Health centres address important urban health issues and work in collaboration with other departments.
- Delayed detection leading to irreversible complications and G2D was observed.
- Leprosy patients present with general health problems and discrimination is not experienced;
- Skin smear facilities were not available at the urban health centre while they were available at the silver jubilee leprosy clinic, a referral facility.
- Patient information documentation (notes are available in the notebook that is available with the patient);
- Patients with reactions were reporting for treatment; reactions were recognized; some were treated and some referred.

➢ Conclusions and recommendations of field visits

The visiting teams made the following recommendations:

- Follow-up is essential for management of reactions (steroids dosing; compliance and completion), neuritis and disability care (foot ulcers may constitute a major concern) and linkages with institutions with specialized care are critical
- Integrating with dermatology clinics is needed for leprosy services
- Reaction management requires detailed workup, involving specialists.
- Post-graduates doctors at medical colleges need to be oriented on the guidelines on leprosy management)
- Importance of skin smear at base-line and during follow-up for measuring prognosis for patients with complications needs to be emphasized
- Guidelines on treatment of lepra reactions needs to be standardized and provided to health staff
- Counselling services need to be established for improving patient compliance and participation in the treatment
- Monitoring of patients on steroids should be improved;
- Assessments are needed for certain groups of patients by occupational therapists.

8. Disability-adjusted life years in leprosy

The concept of DALY was introduced. DALY is the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. The DALY is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. It was developed in the 1990s as a way of comparing the overall health and life expectancy of different countries. DALY is a societal measure of the disease or disability burden in populations. DALY in brief is the sum of years lived with disability and years of life lost. DALY was not considered important in leprosy as the mortality due to leprosy is not significant. Leprosy-related mortality can
occur due to ENL, steroids, dapsone hypersensitivity syndrome. From the patient perspective the disability increases. Patients with ulcers also need to be considered for discussing DALYs in leprosy.

ENL reaction and drug reactions need to be collected for getting actual picture of consequences. Patients with ulcers contribute to DALY. Available literature mainly from one study in India (PSS Rao, 2013) showed there is a reduction of 13.4 years from the ideal productive working life period of life. The study observed that, on average, 30% of the leprosy affected persons work life is lost due to disability. Need to look into how DALYs are worked out for other NTDs was underlined. It was mentioned that Erasmus University is conducting a study on DALYs in leprosy.

The participants concluded that DALY in leprosy should be re-visited. With more information from the Erasmus University study findings, understanding on methods of calculating DALYs in other NTD control programmes and more data pertaining to mortality in leprosy and impact of disability on life of the person affected. WHO to collect data on mortality in leprosy and economic and social impact of disabilities on the persons affected by leprosy due to disabilities.

9. Conclusions and recommendations

Reactions in leprosy are important clinical events (occurring before, during and even after completion of treatment) that influence treatment of patients and affect the quality of life of persons affected by leprosy.

‘Guidelines on Management of Reactions’ should be developed by WHO for use NLPs. They should be based on available evidence with regard to recognizing reactions and treating reactions using steroids and second-line drugs.

A simple tool for identifying new cases of reactions, neuritis and neuropathic pain should be developed for use of frontline health workers.

All patients with reactions and neurological events should be documented and treatments should be monitored once in two weeks.

Adverse events due to MDT or drugs used for the treatment of reactions should also be documented and reported by NLPs.

Mortality associated with reactions (often related to steroid treatment) needs to be documented and national programmes are encouraged to report.

Steroids (oral prednisolone) remain the main choice for treatment for treatment of RR. Frontline health workers need to be trained in recognizing RR and referring them for treatment to referral health facilities.

Erythema nodosum leprosum needs to be recognized in patients and its severity measured. Patients need to be warned that this may be a chronic complication. They need treatment with steroids, but second line drugs should be available so that the morbidity and mortality associated with steroid treatment can be reduced. National programmes should develop recommendations for second-line treatment of ENL.
Use of thalidomide in treating ENL should be reviewed and reinstated as per the WHO Technical Report Series 968, WHO Expert committee on Leprosy Eighth Report 2012.

Silent neuritis and neuropathy (also referred to as Quiet Nerve Paralysis) are important clinical features responsible for development of disabilities.

Nerve function assessment is required for prevention of disabilities. NFA should be introduced at all health facilities treating leprosy and should be done at start and end of MDT, and at any time when there are complaints suggesting reactions and neuritis (NFI of peripheral nerves).

Patients at high risk of developing impairments should be assessed at least every three months during MDT and until one year after release from MDT (at least 9 times for 24 months).

Patients with NFI of less than 6 months duration should be treated with steroids and assessed after 2 weeks and then monthly until the end of the steroid course.

A simple algorithm needs to be developed for use by frontline health workers to screen leprosy patients for identifying patients with high risk for NFI.

A simple format for carrying out NFA needs to be finalized for use by frontline health workers to ensure regular screening of patients to detect impairments at the earliest level.

Calculation of DALYs in leprosy needs further understanding for finalizing a score considering disabilities, mortality due to reactions and discrimination against persons affected by leprosy.

Further research is recommended in the following areas:

- Epidemiology, pathogenesis and treatment of neuropathy in leprosy including silent neuritis and neuropathy
- New drugs and biologicals for treating ENL, RR and neuritis
- Mental health issues in leprosy and its impact on the life of persons affected by leprosy
- Wound care to improve management of plantar ulcers in leprosy
- Assessing impact of reactions using the DALY methodology
- Immunotherapy in leprosy - process documentation and impact assessment
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<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Notes</th>
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<tbody>
<tr>
<td>08:30 – 09:00 hrs</td>
<td><strong>Inaugural session</strong></td>
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<tr>
<td></td>
<td>➢ Welcome – Dr Isabelle Roger WHO</td>
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<td>➢ Message – Dr S K Noordeen</td>
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<td>➢ Opening address by Dr Poonam Khetrapal Singh, Regional Director WHO-SEARO</td>
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<td></td>
<td>➢ Objectives and expected outcomes – Dr V R R Pemmaraju WHO</td>
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<td>➢ Introduction of participants</td>
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<tr>
<td>09:00 – 09:30 hrs</td>
<td>Treatment of reactions and prevention of disabilities – <strong>Current guidance</strong> from WHO – Dr V R R Pemmaraju WHO</td>
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<tr>
<td>09:30 – 10:00 hrs</td>
<td><strong>Group photo; tea/coffee</strong></td>
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<tr>
<td>10:00 – 10:30 hrs</td>
<td><strong>Reversal Reactions</strong>: Data and inputs – Dr Silmara Navarro Pennini, FUAM Brazil</td>
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<tr>
<td>10:30 – 11:00 hrs</td>
<td>Review of literature on treatment practices of reversal reactions – Dr Aparna Srikantam, Blue Peter Leprosy Research Centre India</td>
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<tr>
<td>11:00 – 12:30 hrs</td>
<td><strong>Group work</strong> and presentations</td>
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<td></td>
<td>Clinical features of RR</td>
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<td>Laboratory investigations in management of RR</td>
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<td>Treatment of RR</td>
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<td>Patient records and monitoring of reactions</td>
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<tr>
<td>12:30 – 13:00 hrs</td>
<td>Presentations from groups and recommendations on RR</td>
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<tr>
<td>13:00 – 14:00 hrs</td>
<td><strong>Lunch</strong></td>
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<tr>
<td>14:30 – 14:30 hrs</td>
<td><strong>Erythema nodosum leprosum</strong>: Data and inputs – Dr Mahesh Puri, NLP Nepal</td>
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<tr>
<td>14:30 – 15:00 hrs</td>
<td>Review of literature on treatment practices of ENL reactions – Dr Joydeepa Darlong, TLMTI</td>
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<tr>
<td>15:00 – 16:30 hrs</td>
<td><strong>Group work</strong> and presentations</td>
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<tr>
<td></td>
<td>Clinical features of ENL</td>
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<td>Laboratory investigations in management of ENL</td>
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<td>Patient records and monitoring of ENL</td>
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<td>16:00 – 16:30 hrs</td>
<td><strong>Tea/coffee</strong></td>
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<tr>
<td>16:30 – 17:30 hrs</td>
<td>Presentation from groups and recommendations on ENL</td>
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**Wednesday 12 December 2018**

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<th>Time</th>
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<tr>
<td>08:30 – 11:00 hrs</td>
<td><strong>Field visit</strong> to health facilities and referral leprosy hospital – facilitated by National Institute of Epidemiology, Chennai</td>
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<tr>
<td>11:30 – 12:00 hrs</td>
<td>Reflections from the field visit on reaction management – Dr Manoj Murhekar, NIE Chennai</td>
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<tr>
<td><strong>12:30 – 13:30 hrs</strong></td>
<td>Lunch</td>
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<tr>
<td>13:30 – 14:00 hrs</td>
<td><strong>Neuritis in leprosy</strong>: Data and inputs – Dr Tiffany Tiara Pakasi, NLP Indonesia</td>
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<tr>
<td>14:00 – 14:30 hrs</td>
<td>Review of literature on neuritis and management of neuritis – Dr Saba Lambert, ALERT Ethiopia</td>
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<tr>
<td>14:30 – 15:00 hrs</td>
<td>Silent neuritis – Professor M D Gupte, Chair WHO TAG</td>
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<tr>
<td><strong>15:00 – 15:30 hrs</strong></td>
<td>Tea/coffee</td>
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<tr>
<td>15:00 – 16:30 hrs</td>
<td><strong>Group work</strong> and presentations</td>
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<tr>
<td></td>
<td>Clinical features of neuritis</td>
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<td>Laboratory investigations in management of neuritis</td>
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<td>Treatment of neuritis</td>
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<td>Patient records and monitoring of neuritis</td>
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<tr>
<td>16:30 – 17:30 hrs</td>
<td>Presentation from groups and recommendations on neuritis</td>
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**Thursday 13 December 2018**

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<th>Time</th>
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<tr>
<td>08:30 – 09:00 hrs</td>
<td><strong>Nerve function assessment</strong> and prevention of disabilities: Data and inputs – from The Philippines National Programme – NPM The Philippines</td>
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<tr>
<td>09:00 – 09:30 hrs</td>
<td><strong>NFA tools</strong>: Review of literature and data – NLEP India</td>
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<td>Prevention of impairment and disability programmes – Dr Kingsley Stanley, ALERT India</td>
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<td><strong>09:30 – 10:00 hrs</strong></td>
<td>Tea/coffee</td>
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<tr>
<td>10:30 – 12:00 hrs</td>
<td><strong>Group work</strong> and presentations</td>
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<td>NFA frequency and procedure</td>
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<td>Tools/formats for carrying out NFA</td>
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<td>Patient records and monitoring of NFA</td>
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<tr>
<td>12:00 – 13:00 hrs</td>
<td>Presentations from groups and recommendations on algorithm of NFA</td>
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<tr>
<td><strong>13:00 – 14:00 hrs</strong></td>
<td>Lunch</td>
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<tr>
<td>14:00 – 14:30 hrs</td>
<td><strong>DALYs in leprosy</strong>: Discussion for further steps - Professor M D Gupte</td>
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</tbody>
</table>
| 14:30 – 16:30 hrs | Presentations and discussions on technical guidance on treatment of RR, ENL, neuritis and NFA – Moderator - Dr Manoj Murhekar  
|                 | Presentations by Working Groups on RR, ENL, neuritis and NFA          |
| **16:00 – 16:30 hrs** | Tea/coffee                                                              |
| 16:30 – 17:00 hrs | **Conclusions and recommendations**                                   |
| 17:00 – 17:15 hrs | **Closing session**                                                    |
Annex 2: List of participants

**National Leprosy Programmes**

Dr Silmara Navarro Pennini  
Fundação Alfredo da Matta  
Manaus, Brazil  
Representative (State Level)  
National Leprosy Eradication Programme  
Ministry of Health and Family welfare  
New Delhi, India

Dr Tiffany Tiara Pakasi  
Head, Leprosy Section  
Ministry of Health  
Jakarta, Indonesia

Dr Srf Linuwih Susetyo Wardhani  
Directorate General of Prevention and Disease Control  
Ministry of Health  
Jakarta, Indonesia

Mr Mahesh Puri  
Tuberculosis Leprosy Officer  
Ministry of Health and Population  
Kathmandu, Nepal

Dr Nicholas Negia Agebigo  
Port Moresby General Hospital  
Papua New Guinea

Dr Faith Daphne H Estrada  
Western Visayas Sanitarium  
Barangay Inangayan, Santa Barbara  
Iloilo, The Philippines

Dr Ken Jetton,  
Ministry of Health and Human Services  
Majuro, Marshall Islands

Dr Elizabeth Keller  
Physician for tuberculosis, Hansen Disease and noncommunicable diseases  
Pohnpei State Government  
Pohnpei, Federated States of Micronesia

**Experts**

Dr Temea Bauro  
General Medical Doctor  
Ministry of Health and Medical Services  
Tarawa, Kiribati

Dr S K Noordeen  
Chennai, India

Dr Linda F Lehman  
Senior Advisor for Morbidity Management and Disability Prevention  
American Leprosy Missions  
Belo Horizonte, Brazil

Dr Saba Lambert  
All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre  
Addis Ababa, Ethiopia

Professor Ousmane Faye  
Department of Dermatology  
Centre national d'appui à la lutte contre la maladie  
Bamako, Mali

Dr Abdoulaye Fomba  
Service of Leprology  
Bamako, Mali

Professor Diana Lockwood  
Department of Clinical Research  
London School of Hygiene and Tropical Medicine  
London, United Kingdom of Great Britain and Northern Ireland

Mr Kingsley Stanley  
ALERT India  
Navi Mumbai, India

Dr V V Pai  
Bombay Leprosy Project  
Mumbai, India
Dr Jerry Joshua
Schieffelin Institute of Health Research and Leprosy Centre
Karigiri, India

Dr Vanaja Shetty
Foundation for Medical Research
Mumbai, India

Dr Aparna Srikantam
Blue Peter Leprosy Research Centre
Hyderabad, India

Dr Joyadeeepa Darlong
The Leprosy Mission Trust India
New Delhi, India

Dr Manoj Murhekar
National Institute of Epidemiology
Chennai, India

Mr V Narasappa
Association of People Affected by Leprosy
Hyderabad, India

Dr Roch Christian Johnson
Université d’Abomey-Calavi
Benin

Observers

Ms Aya Tobiki
Sasakawa Memorial Health Foundation
Tokyo, Japan

Ms Kyoko Itoh
The Nippon Foundation
Tokyo, Japan

WHO TAG members

Professor Mohan D Gupte
Pune, India

Dr Carlos Wiens
Asunción, Paraguay

Dr Paul Saunderson
American Leprosy Missions
Alesund, Norway

WHO Secretariat

Dr V R R Pemmaraju
Global Leprosy Programme
WHO Regional Office for South-East Asia

Dr Isabelle Roger
Regional Advisor, Neglected Infectious Diseases and Leprosy
PAHO/WHO Country Office for Brazil

Dr Zaw Lin
Technical Officer, Neglected Tropical Diseases
WHO Regional Office for South-East Asia
Reactions are acute exacerbations of signs and symptoms of leprosy occurring during the natural history of the disease affecting skin, nerves, eyes or limbs. Left untreated or improperly managed, reactions can lead to nerve function impairment and subsequently to disabilities. Reactions and neuritis remain an enigma for many frontline health staff treating leprosy. The problem is more noticeable in an integrated health care setting. Data collected from national leprosy programmes showed that, in 2017, 7332 patients were treated for Type 1 Reaction (also known as Reversal Reaction) and 5370 patients have been treated for Type 2 Reaction (also known as erythema nodosum leprosum).

Prevention of disabilities starts with early detection of reactions, prompt recognition of nerve function impairment and effective treatment of neuritis. These are the essential steps during the management of the disease for ensuring good quality and holistic treatment to persons affected by leprosy. The most recent World Health Organization technical guidance on treatment of reactions and prevention of disabilities dates from 2010. Since then approaches to managing reactions have further improved. This informal consultation reviewed available evidence on treatment practices followed for managing reactions in leprosy. Recommendations for treatment of reactions were made to guide leprosy programmes in the field.