



Leprosy reactions: New knowledge on pathophysiology, diagnosis, treatment and prevention

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Abstract

Leprosy, or Hansen's disease, caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, is a chronic granulomatous infectious disease. Leprosy reactions, characterised by neurocutaneous inflammation, complicate the disease's indolent course, leading to significant morbidity. However, limited knowledge of reaction pathophysiology stems from a lack of experimental models and the abrupt onset of reactional episodes, posing challenges in delineating initial pathogenic steps. In type 1 reactions, ongoing studies explore the roles of interferon-gamma which results in increased interleukin (IL)-15 and autophagy. Leprosy reactions also exhibit an increase in T helper 17 (Th17) and a decrease in T-regulatory cell (Treg) populations, resulting in diminished tumour growth factor-beta and heightened IL-6 and IL-21 production. Exploring the pathogenesis of erythema nodosum leprosum (ENL) reveals insights into neutrophils, Toll-like receptor 9, B-cells, myeloid-derived suppressor cells, IL-10 pathway and neurotrophins. Noteworthy therapeutic targets include increased expression of cyclooxygenase 2 and vascular endothelial growth factor. Early reaction diagnosis is crucial to limit neural damage, with high-resolution ultrasonography showing promise in detecting minimal nerve involvement. Therapies for ENL management, such as thalidomide, methotrexate, apremilast, minocycline and tumour necrosis factor-alpha inhibitors, hold potential. This review addresses recent advances in leprosy reaction pathogenesis and diagnostics, offering therapeutic insights and preventive strategies to mitigate their onset.

Key words: Leprosy, Hansen disease, leprosy reactions, reversal reactions, erythema nodosum leprosum, type 1 reaction, type 2 reaction

Introduction

Leprosy reactions are acute immunologically driven episodes in the chronic course of leprosy that result in significant functional morbidity. These may occur prior to, during or following the completion of multidrug therapy (MDT), with a reported lifetime prevalence of nearly 50% among leprosy patients.^{1,2} Two major types of leprosy reactions include reversal reactions (RRs) or type 1 reaction (T1R) and erythema nodosum leprosum (ENL) or type 2 reaction (T2R). RRs are seen in up to one-third of patients in the borderline spectrum of leprosy.³ RRs are type IV hypersensitivity reactions due

to an increase in cell-mediated immune response (CMI) against *Mycobacterium leprae* (*M. leprae*). ENL occurs in 50% of patients with lepromatous leprosy (LL) and 10% of patients with borderline lepromatous (BL) leprosy.⁴ ENL can be classified based on its duration and recurrence. Acute ENL refers to an episode lasting less than six months, with treatment gradually tapered off and no recurrence while on therapy. Recurrent ENL involves a new episode occurring at least 28 days after completing treatment for a prior episode, while chronic ENL persists beyond six months, requiring continuous treatment or having treatment-free intervals shorter

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than 28 days. ENL is a type III hypersensitivity reaction with deposition of immune complexes, neutrophilic infiltrate and increased levels of circulating tumour necrosis factor-alpha (TNF- α). Lack of a satisfactory animal model that reproduces the whole spectrum of leprosy and reactional episodes is a major limitation in understanding the pathophysiology of the disease.

Pathophysiology

Type 1 reaction

T1R is a condition characterised by T-cell hypersensitivity against *M. leprae* in the borderline spectrum of leprosy. Upon *M. leprae* inoculation in the nasal mucosa, the immune response is initiated involving phagocytosis by antigen-presenting cells (APCs). These APCs capturing antigens from peripheral tissues migrate to lymph nodes, where they stimulate the adaptive immune response through major histocompatibility complex class II (MHC-II) molecules and two signals to naïve CD-4+ T helper (Th) cells. Interleukin (IL)-12 production by APCs promotes immune activation by differentiating CD4+ T-cells into effector Th cells. Effector Th cells release IL-2, stimulating the proliferation of Th cells and CD8+ T-cells. These activated T-cells migrate back to

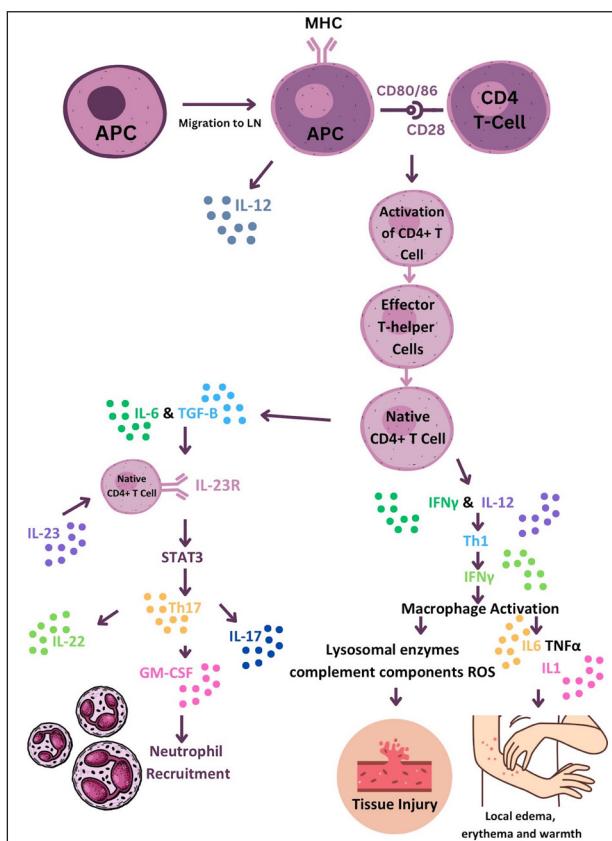


Figure 1: Diagram illustrating the immune response to *M. leprae* in Type 1 reaction that leads to erythema, oedema and tissue injury. (APC: Antigen-presenting cell, CD4: Cluster of differentiation 4, GM-CSF: Granulocyte-macrophage colony-stimulating factor, IFN: Interferon, LN: Lymph node, MHC: Major histocompatibility complex, MHC II: Major histocompatibility complex class II, STAT3: Signal transducer and activator of transcription 3, TGF: Transforming growth factor.)

peripheral tissues, where CD8+ T-cells release perforin and granzymes, damaging myelin sheath and Schwann cells.³ Naïve T-cells differentiate into Th17 cells due to IL-6 and tumour growth factor-beta (TGF- β) production by APCs. IL-17 from activated Th17 cells aids neutrophil recruitment. Interferon-gamma (IFN- γ) from APCs activates macrophages, leading to pro-inflammatory cytokine production (TNF- α , IL-1 β , IL-6). IL-6 is thus produced by both APCs and activated macrophages and underlies the inflammatory process. Figure 1 illustrates the pathogenesis of T1R. TNF- α and IFN- γ directly stimulate nerve fibres, causing neuritis in type I reactions [Figure 2].⁵ This inflammatory environment, coupled with mycobacterial killing and antigenic spread, determines the progression of reactional episodes.

Heat shock proteins (HSPs), expressed during chronic inflammation and stress, may induce autoimmune reactions during mycobacterial infections due to molecular mimicry with host proteins. Studies have identified B-cell mimicking epitopes shared between *M. leprae*'s HSP65 and host keratin, finding significantly higher antibody levels against specific HSP peptides in T1R patients compared to non-reaction individuals and healthy controls.^{6,7} These findings suggest potential predictive biomarkers for T1R and highlight the role of molecular mimicry in leprosy-induced immune responses. Unconventional T-cells are proposed to mediate the interface between innate and adaptive immunity in T1Rs. Pathak *et al.*

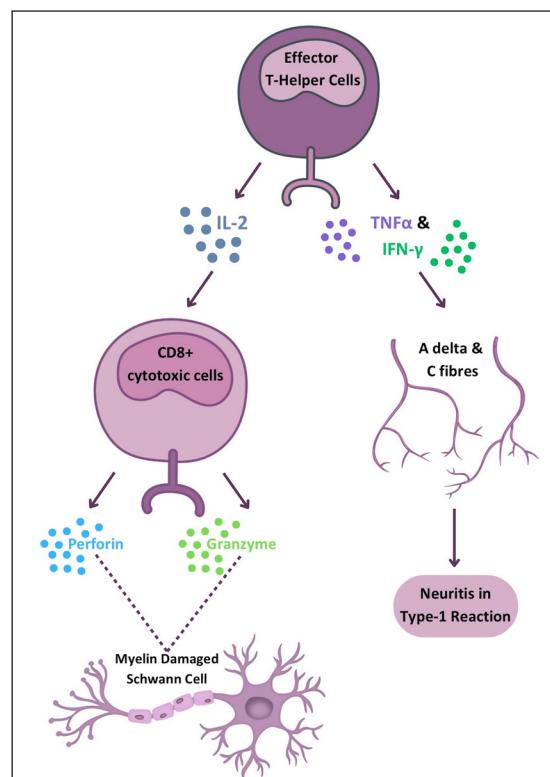


Figure 2: Diagram illustrating the immune response in Type 1 reaction leading to neuritis and nerve damage. (CD8: Cluster of differentiation 8, IFN: Interferon, IL: Interleukin, TNF: Tumour necrosis factor.)

revealed decreased $\gamma\delta$ T-cell numbers and elevated NKT-like and NK cells in T1R patients compared to non-reaction individuals.⁸

IFN- γ is pivotal in T1Rs, with studies identifying increased IL-15 production and autophagy activation as downstream effects.⁹ Comparative gene expression analysis between T1R skin lesions and *M. leprae* + IFN- γ stimulated macrophages revealed 13 common genetic elements, including the autophagy regulator translocated promoter region (TPR), significantly increased in macrophages from T1R patients.⁹ Autophagy is crucial for inflammasome component degradation, limiting exaggerated inflammatory responses. Tuberculoid leprosy patients exhibit upregulated autophagy genes compared to lepromatous cases.¹⁰ Autophagy is upregulated by dead bacilli, while live mycobacteria inhibit it, serving as an immune escape mechanism.¹⁰ Downregulation of autophagy genes, along with TLR3 and NLRP3-IL-1 β pathway overexpression in multibacillary (MB) patients, increases RR risk.¹¹ Blocking autophagy with 3-methyladenine in *M. leprae*-stimulated monocytes enhances NLRP3 inflammasome expression and subsequent IL-1 β and IL-6 production.¹¹ Pro-autophagic drugs may help control bacillary load and potentially treat T1Rs.

Th17 population increases and T-regulatory cell (Treg) population reductions are observed in leprosy reactions, with decreased TGF- β and increased IL-6 and IL-21 production.^{12,13} IL-21 is crucial in T1R pathogenesis by promoting the differentiation of T-regulatory cells into the Th17 pathway, evidenced by its higher levels in T1R patients' blood and skin

lesions, positive correlation with Th17 markers, and negative correlation with Treg markers.¹⁴ Table 1 summarises novel mechanisms in T1R pathogenesis.

Type 2 reactions

The pathogenesis of T2R involves type III hypersensitivity due to inadequate clearance of antigen-antibody complexes, resulting in inflammation and leukocyte chemotaxis. Skin biopsies of ENL patients show complement and immunoglobulin deposition in the dermis, similar to an Arthus reaction.¹⁵ Figure 3 illustrates the current knowledge regarding immunopathogenesis of T2R.

Neutrophils play a central role in ENL pathogenesis, with Tavares *et al.* highlighting elevated low-density neutrophils (LDNs) in ENL patients.¹⁶ Neutrophil extracellular traps (NETs), significant in severe autoimmune disorders, are abundant in ENL patients and reduced by thalidomide.^{17,18} The balance between IL-10 and TNF- α in neutrophils, along with Toll-like receptor 9 (TLR9) recognition of DNA, offers potential biomarkers for ENL.^{19,20} Further investigation revealed the upregulation of plasmacytoid dendritic cell/type 1 interferon pathway, as a consequence to increase in TLR9 expression.²¹ B-cell subpopulation alterations^{22,23} and myeloid-derived suppressor cells with elevated annexin A1 levels may impact T-cell efficacy.²⁴ Depleting CD25+ cells reversibly impairs immune response, highlighting Tregs as a potential therapeutic target.²⁵ Neurotrophins, particularly nerve growth factor (NGF), showed decreased levels and the presence of autoantibodies modulated by cyclosporin

Table 1: Novel mechanisms implicated in the pathophysiology of type 1 leprosy reactions

Pathogenetic mechanism	Role in type 1 reaction	Evidence
Molecular mimicry	Monoclonal antibodies against <i>M. leprae</i> have been reported to cross-react with human nerve and skin components, suggesting a potential contribution to the development of autoimmune clinical manifestations in leprosy	Molecular mimicry between cytokeratin-10 and HSP65 reported; elevated antibodies against HSP4 and HSP5 in type 1 reaction patients ^{6,7} Differential antibody levels against mimicking peptides potentially predictive biomarkers for T1R development and leprosy disease
Unconventional T-cells	Mediating interface between innate and adaptive immunity	Significant decrease in $\gamma\delta$ T-cell numbers; elevated frequencies of NKT-like and NK cells in type 1 reactions ⁸ Additionally, higher plasma levels of TNF α , IL1 β , IL17 and CXCL10; increased gene expression of IFN γ , IP10, TNF α , IL6 and IL17A; upregulated chemokines like CCL3, CCR1, CCR5 and CXCR3 in Type 1 reaction patients ⁸
Autophagy	Essential for inflammasome component degradation, limiting exaggerated inflammatory responses Downregulation of autophagy genes increases the risk of reversal reactions	Comparative gene expression analysis revealed common genetic elements, including autophagy regulator TPR ⁹ Upregulated autophagy genes in tuberculoid leprosy ¹⁰ Live mycobacteria inhibit autophagy ¹⁰ Downregulation of autophagy genes and TLR3, NLRP3-IL-1 β pathway overexpression increase risk of reversal reactions ¹¹ Blocking autophagy enhances NLRP3 inflammasome expression ¹¹
Th17 and Treg population alterations	Increase in Th17 and reduction in Treg populations observed	IL-21, a differentiating cytokine promoting T-regulatory cells to Th17 pathway, explored ¹⁴ IL-21+ cells significantly higher in T1R patients; gene expression of IL-21 correlates positively with Th17 cell markers and negatively with Treg cell markers ¹⁴

HSP: Heat shock protein, TNF- α : Tumour necrosis factor-alpha, IL1 β : Interleukin 1-beta, IL17: Interleukin 17, CXCL10: C-X-C Motif Chemokine Ligand 10, IFN γ : Interferon-gamma, IP10: Interferon-gamma-induced protein 10, IL6: Interleukin 6, IL17A: Interleukin 17A, CCL3: C-C Motif chemokine ligand 3, CCR1: C-C chemokine receptor type 1, CCR5: C-C chemokine receptor type 5, CXCR3: C-X-C chemokine receptor type 3, TPR: Translocated promoter region, TLR3: Toll-like receptor 3, NLRP3: Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3, Th17: T-helper 17 cell, Treg: Regulatory T-cell, NKT: Natural killer T-cells.

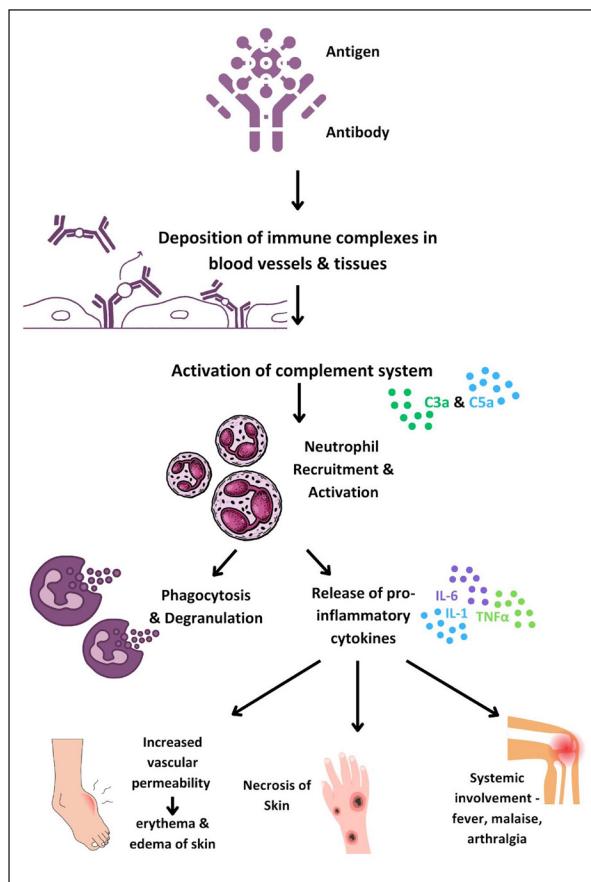


Figure 3: Diagram illustrating the immunopathogenesis of type 2 reactions.

A, suggesting targets for neuroimmune reaction control.²⁶ Table 2 summarises recent breakthroughs in ENL and their therapeutic implications.

Infections are potential triggers for lepra reactions. Motta *et al.* found that 39% of patients with lepra reactions had concurrent infections, mainly oral.²⁷ A thorough search based on patient history and clinical examination is advisable, especially in recurrent reactions. However, the impact of specific infections remains uncertain, as a scoping review did not indicate a higher incidence of reactions in patients with concurrent bacterial, fungal or parasitic infections.²⁸

A recent study highlighted the different roles of dead and viable bacilli in the modulation of lepra reactions and nerve damage. While viable bacilli promote its own survival by exploiting the host cells, dead bacilli create a pro-inflammatory milieu and promote nerve damage.²⁹

Diagnosis

Early diagnosis of reactions is essential to limit the resulting neural damage. Clinical examination remains the cornerstone of the diagnosis of a reaction once it manifests. Classically, T1R presents with erythema and oedema of pre-existing lesions which may or may not be associated with neuritis. ENL manifests as evanescent, tender nodules, more often

associated with systemic complaints like fever, joint pain, bone pain, and lymphadenopathy. Erythema Nodosum Leprosum International STudy (ENLIST) score is used frequently to classify it as mild, moderate or severe, which determines the management. There is an urgent need to identify biomarkers that may predict the course of the disease and identify patients who are at increased risk of developing reactional episodes. Currently, there is no diagnostic tool that reliably predicts the onset of reactions before clinical manifestations occur. Table 3 summarises the newer diagnostic modalities with a possible role in leprosy reactions.

Nerve conduction study (NCS) is established for detecting neural dysfunction. Recent studies suggest high-resolution ultrasonography (HRUS) with colour Doppler (CD) can aid in diagnosing leprosy reactions, especially in patients with minimal nerve involvement or lacking a motor response in NCS.³⁰ Magnetic resonance imaging (MRI) helps diagnose nerve abscesses, distinguish leprosy reactions from other causes of nerve thickening and detect the central nervous system involvement.³¹⁻³³ Dermoscopy is another easily available non-invasive imaging which has been utilised in leprosy reactions.^{34,35} Table 3 outlines the dermoscopic features of lepra reactions.

Higher titres of antibodies against natural octyl disaccharide-leprosy IDRI diagnostic (anti-NDO-LID) at baseline have been associated with the risk of future ENL.³⁶ An observational study showed that patients with ENL had 66.66% higher titres of antibodies against Phenolic Glycolipid-1 (anti-PGL-1) and 91.66% higher titres of anti-NOD-LID-1 as compared to those without reactions.³⁷ Further, positivity for both antibodies was significantly associated with the likelihood of developing reactions in the future. Another study revealed anti-PGL1 to be an important prognostic factor for the prediction of leprosy reactions.³⁸ Additionally, salivary antibodies to lipoarabinomannan (LAM) antigen may be used as a tool to monitor patients undergoing treatment to predict reactional episodes.³⁹

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) have been utilised to assess the inflammatory response in various diseases. Gomes *et al.* assessed the utility of assessing NLR in patients with leprosy reactions.⁴⁰ The NLR cut-off for the diagnosis of any leprosy reaction was 2.75 (sensitivity 61.0%, specificity 92.0%, accuracy 77.0%) while the cut-off for T2R was 2.95 (sensitivity 81.0%, specificity 74.0%, accuracy 78.0%). Another study noted that NLR and PLR but not LMR were useful as a diagnostic biomarker for ENL.⁴¹

Complement component 1q (C1q), a key component of the classical complement pathway, has been studied as a diagnostic and monitoring parameter for ENL.⁴² C1q levels in peripheral blood were significantly lower in untreated

Table 2: Summary of recent studies on pathogenesis of erythema nodosum leprosum

Study	Salient findings	Implications
Tavares <i>et al.</i> ¹⁶	Flow cytometry of ENL patients demonstrated elevated frequency of LDN, which displayed a neutrophilic-activated phenotype Higher CD11b and lower CD62L surface expressions on LDNs correlate with the activation status of LDNs ENL patients under thalidomide treatment presented similar frequency of LDNs as observed before treatment but its activation status was lower	Potential biomarkers for diagnosis and monitoring of reactional states
Pacheco <i>et al.</i> ¹⁹	Patients with ENL had a subpopulation of neutrophils that expressed IL-10R1 in both skin lesions and blood Neutrophils found in the blood of ENL patients were able to secrete detectable levels of TNF- α , which could be blocked by the addition of IL-10	IL-10R1 is a possible biomarker in ENL IL-10 pathway may be a therapeutic target for the management of ENL
Dias AA <i>et al.</i> ²⁰	DNA sensing via TLR-9 constitutes a major innate immunity pathway involved in the pathogenesis and evolution of ENL	TLR-9 antagonists are potential alternative to more effectively treat ENL
Da Silva <i>et al.</i> ¹⁸	Abundant NETs were found in T2R skin lesions and increased spontaneous NETs formation was observed in T2R peripheral neutrophils. TLR9 expression was shown to be higher in T2R neutrophils Treatment of T2R patients with thalidomide for seven consecutive days resulted in a decrease in all of the evaluated in vivo and ex vivo NETosis parameters.	DNA recognition via TLR9 may be one of the pathways triggering this process during T2R, thus it is a potential therapeutic target
Nogueria <i>et al.</i> ²²	Compared to uninfected subjects, an increase in mature B-cells and a decrease in memory B-cells was observed in MB disease and ENL Decrease in atypical B-cells (CD27-CD21-) and an increase in activated B-cells (CD27+ CD21+) was noted during ENL episodes	First study to describe the different B-cell phenotypes in polar forms of leprosy and in ENL
Negera <i>et al.</i> ²⁵	Increase in activated memory B-cells and reduced number of tissue-like memory B-cells in untreated ENL patients as compared to LL patient The percentage of total circulating B-cells was similar among ENL patients and non-reactional LL patients; however, proportion of B-cells was significantly reduced by treatment for ENL	B-cell depletion may have a role in management of ENL
Da Silva <i>et al.</i> ²⁴	An increased density of myeloid-derived suppressor cells has been observed in patients with lepromatous leprosy and T2R Presence of annexin A1 was observed in all myeloid-derived suppressor cells. Monocytic myeloid-derived suppressor cell in the lepromatous patients had particularly higher levels of this protein when compared to the reactional patients	High annexin A1 expression in lepromatous patients may be responsible for reduction in the efficacy of T-cell action against <i>M. leprae</i> , rendering the patient susceptible to MB disease
Jesus <i>et al.</i> ²⁶	NGF is decreased in the course of leprosy and there is presence of autoantibodies against NGF in all clinical forms of leprosy and neuroimmune reactions Levels of autoantibodies against NGF are decreased by the immunomodulatory activity of cyclosporin A, which mainly controls pain and improves motor function and sensitivity	Suppression of anti-NGF and the regulation of NGF levels can be attractive targets for immunomodulatory treatment and for controlling the neuroimmune reactions of leprosy
Negera <i>et al.</i> ²⁵	Tregs in ENL maintain suppressive function despite reduced numbers Depletion of Tregs enhances TNF α and IFN γ responses, indicating a regulatory role	Tregs emerge as potential targets for immune modulation in leprosy
Castro <i>et al.</i> ¹³	Decrease in CD4+TGF- β + Treg and CD8+ TGF- β + Treg cells Upregulation of IL-17 and IL-6	Enhances our understanding of immune hyporesponsiveness in MB patients and hyperresponsiveness in reactions
Rosa <i>et al.</i> ²¹	Increased type 1 IFN expression Decreased frequency of peripheral pDC	pDC/type I IFN pathway may be utilised as potential biomarker for diagnosis Targeting pDC may be a viable therapeutic approach in ENL

B-cells: B lymphocytes, CD11b: Cluster of differentiation 11b, CD21: Cluster of differentiation 21, CD27: Cluster of differentiation 27, CD62L: Cluster of differentiation 62L, ENL: Erythema nodosum leprosum, IFN: Interferon, IL-10: Interleukin-10, IL-10R1: Interleukin-10 receptor subunit alpha, LDNs: Low-density neutrophils, MB: Multibacillary, NETs: Neutrophil extracellular traps, NGF: Nerve growth factor, pDC: Plasmacytoid dendritic cells, T2R: Type 2 reaction, TLR-9: Toll-like receptor 9, TNF- α : Tumour necrosis factor alpha

ENL patients compared to LL controls. Additionally, increased genetic expression of C1q components was noted in ENL patients' peripheral blood and skin biopsies, which normalised after treatment, suggesting C1q as a potential diagnostic marker and treatment response indicator for ENL. An immunohistochemical study also found significantly increased expression of cyclooxygenase 2 and vascular endothelial growth factor in dermal macrophages and

vascular endothelium in T1Rs, followed by T2Rs, compared to controls.⁴³

Pentraxin-3 (PTX-3), an inflammatory marker, is higher in MB patients before and during acute ENL and decreases within seven days of thalidomide therapy.⁴⁴ A novel study used RNA expression analysis of 1090 whole blood samples to profile 103 target genes for innate and adaptive immune

Table 3: Newer diagnostic modalities with possible role in leprosy reactions

Type of diagnostic modality	Specific investigation	Results	Role in leprosy reactions
Non-invasive imaging	Dermoscopy ³⁵	T1R: intense erythema, large telangiectatic vessels, violaceous to brown periappendageal pigmentation, white globules, epidermal scaling, follicular plugging T2R: erythema, vascular dilation, red dots, hypopigmented structureless areas	Diagnosis of leprosy reactions
	HRUS with colour Doppler ³⁰	Blood flow detected on colour Doppler in patients with nerve involvement in NCS and in those with minimal or no changes in NCS	Diagnosis of neural involvement in leprosy reactions with minimal nerve involvement or those lacking a motor response in NCS
	Magnetic resonance imaging ³¹⁻³³	Leprosy-associated peripheral nerve abscess usually reveals signal changes of an abscess with peripheral contrast enhancement of the abscess wall and inflammatory thickening of the whole nerve trunk Rarely, CNS lesions may also be diagnosed by MRI	Differentiating many mass lesions of peripheral nerves such as a schwannoma, neurofibroma and more from leprosy-associated abscess or cranial nerve involvement
Serology for <i>M. leprae</i>	Anti-PGL-1 antibody ³⁷	Moderate sensitivity and specificity for predicting future reactions	May predict risk of future ENL episodes, but not type 1 reaction
	Anti-NDO-LID-1 antibody ³⁷	Good sensitivity and specificity for predicting future reactions	
	Anti LAM salivary antibody ³⁹	Similar odds of predicting reaction as anti-PGL-1 antibody	
Inflammatory markers	NLR, PLR and LMR ⁴¹	Fair sensitivity and specificity in diagnosis of leprosy reactions	Diagnosis and possibly response to anti-inflammatory therapies
	C1q ⁴²	Lower level during ENL, with normalization after treatment	Diagnosis of leprosy reactions and monitoring response to treatment
	Cyclooxygenase 2 and vascular endothelial growth factor expression in dermal macrophages and vascular endothelium ⁴³	Higher in type 1 followed by T2R compared to controls	Potential targets for treatment of lepra reactions
	Pentraxin-3 ⁴⁴	Elevated prior to onset and during acute ENL, declined after treatment	Prediction of predisposition to ENL, diagnosis of ENL and monitoring response to therapy
Molecular diagnosis	Dual colour reverse-transcription multiplex ligation-dependent probe amplification ⁴⁵	A transcriptomic signature of risk for reversal reactions consisting of five genes (<i>CCL2</i> , <i>CD8A</i> , <i>IL2</i> , <i>IL15</i> and <i>MARCO</i>) was identified based on cross-sectional comparison of RNA expression	Could predict reversal reactions at least two weeks before onset

Anti-LAM salivary antibody: Antibodies against lipoarabinomannan, Anti-NDO-LID-1 antibody: Anti-natural octyl disaccharide-leprosy IDRI diagnostic, Anti-PGL-1 antibody: Antibodies against Phenolic Glycolipid 1, C1q: Complement 1q, CNS: Central nervous system, ENL: Erythema nodosum leprosum, HRUS: High resolution ultrasound, LMR: Lymphocyte-to-monocyte ratio, MRI: Magnetic resonance imaging, NCSs: Nerve conduction studies, NLR: Neutrophil-to-lymphocyte ratio, Pentraxin-3: Pentraxin-related protein 3, PLR: Platelet-to-lymphocyte ratio, T1R: Type 1 reaction, T2R: Type 2 reaction

responses.⁴⁵ A transcriptomic signature of five genes (*CCL2*, *CD8A*, *IL2*, *IL15*, *MARCO*) was identified, predicting RRs at least two weeks before onset.⁴⁵ Other potential ENL diagnostic biomarkers include *IL-6*, *IL-7*, *CCL-11*, alpha-1 acid glycoprotein and *CD-64*.⁴⁶ No single marker or a set of markers has shown to reliably and effectively prognosticate the occurrence of lepra reactions.

The Specialist System for Evaluation of Risk of Occurrence of Reactional States in Leprosy (SEPARH) is an online tool that predicts leprosy reactions with up to 87.7% accuracy using socio-demographic details, family history, clinical, laboratory and genetic data.⁴⁷

Treatment

Type 1 reactions

The objective of treatment for T1R is control of neural inflammation and prevention of further immune-mediated

damage. For mild T1R, non-steroidal anti-inflammatory drugs may suffice, but severe reaction, especially with neuritis, requires medical and/or surgical treatment. Current evidence suggests that oral corticosteroids are the mainstay for severe T1Rs and should be started in a dose of 0.5–1 mg/kg/day and gradually tapered to zero over a span of 20 weeks [Figure 4]. A randomised trial (Treatment of Early Neuropathy in Leprosy or TENLEP) compared oral corticosteroids for 20 and 32 weeks in patients with recent onset nerve function impairment (less than six months duration), including T1R.⁴⁸ No difference in clinical outcomes was noted between the groups at the end of the study period.

Other immunosuppressive agents that have been used successfully for the management of T1R include cyclosporine and methotrexate.⁴⁹⁻⁵¹ A recent review and systematic analysis has highlighted the role of methotrexate in type 1 and 2

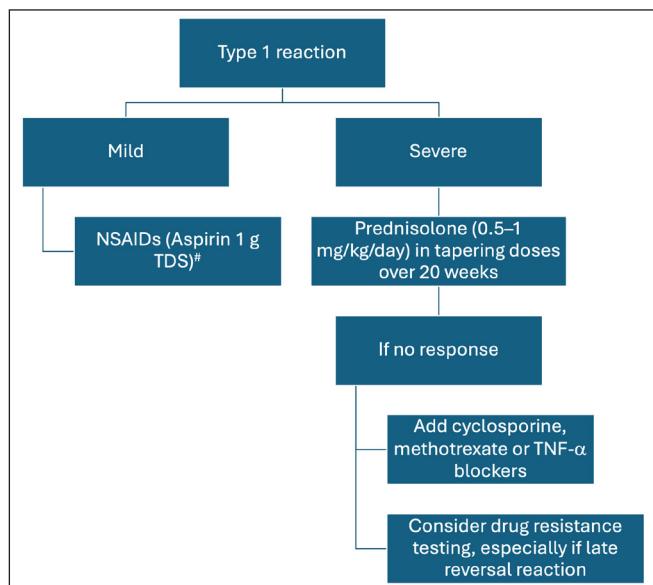


Figure 4: Management of type 1 leprosy reactions (NSAIDs: Non-steroidal anti-inflammatory drugs, TDS: Ter Die Sumendum or thrice a day, TNF- α : Tumour necrosis factor alpha). [#]Consider combination with proton pump inhibitors to mitigate associated gastrointestinal adverse effects.

lepra reactions. The study recommends lower doses of methotrexate than the dose used in autoimmune diseases and its combination with low-dose steroids.⁵² A combination of azathioprine with prednisolone was not found to be superior over prednisolone alone.⁵³ Further, incidence of anaemia was increased by a combination of azathioprine and dapsone.

Successful use of infliximab as a therapy for RR was reported recently in a patient with steroid-dependent neuritis.⁵⁴ A dramatic and lasting remission was noted after three infliximab infusions at week 0, 1 and 6. However, it must be noted that infliximab has been implicated in causing neuritis and demyelination, and should be used with utmost caution in a patient with nerve function impairment. In cases of recalcitrant neuritis or nerve abscess, surgical decompression may be warranted, based on the physician's discretion.⁵⁵

Type II reactions

Figure 5 summarises the management of T2R. Rest and non-steroidal anti-inflammatory agents are the cornerstone therapy for mild ENL. Use of corticosteroids is recommended by WHO guidelines for severe ENL⁵⁶; however, it is associated with several adverse effects, which may be minimised by splitting the dose of oral corticosteroids.⁵⁷ Thalidomide is an effective and rapidly acting therapy for severe ENL that acts by inhibition of TNF- α . Its use is restricted by potential teratogenicity, neuropathy and limited availability. A recent real-world study demonstrated the low-dose thalidomide (25–150 mg/day) to be as efficacious as the high-dose regimen.⁵⁸ Clofazimine is another important agent for the management of chronic ENL; however, the slow onset of action limits its use in cases of severe/acute ENL. Two pilot studies from Ethiopia analysed the role of cyclosporine in the management

of ENL.⁴⁹ Cyclosporine demonstrated potential benefits in acute ENL, reducing severity and prednisolone requirement, but showed less efficacy in chronic ENL, leading to earlier and more severe flare-ups requiring higher prednisolone doses. There is an unmet need for safe and effective therapies for the management of ENL.

Several therapies show promise in ENL, including methotrexate, apremilast, minocycline, colchicine and TNF- α inhibitors. A review of 21 patients treated with methotrexate (7.5–20 mg) found it safe and effective for leprosy reactions when combined with low-dose corticosteroids.⁵⁹ Its role in ENL was highlighted in a recent trial, though the lack of controlled studies makes standard dosage protocols difficult.⁵² It is particularly useful for patients with steroid contraindications like diabetes. An ongoing trial (MaPs in ENL) is assessing methotrexate's efficacy in ENL.⁶⁰ However, careful patient selection is needed due to potential overlap with dapsone induced side effects and methotrexate side effects like anaemia and liver issues.⁶¹

In a case series of six ENL patients, etanercept combined with corticosteroids reduced steroid dosage by 42%.⁶² A systematic review found four reports of ENL successfully treated with infliximab or etanercept,⁶³ but also noted ten cases of leprosy following TNF- α inhibitor use, suggesting a risk of leprosy infection or reactivation of subclinical infection.⁶³

Apremilast, a phosphodiesterase-4 inhibitor, reduces pro-inflammatory cytokines, like TNF- α and IL-12/23, involved in ENL pathogenesis. Case reports and series have shown its successful use in chronic and recurrent ENL.^{64–66} Minocycline, an antibacterial and anti-inflammatory agent, is used as a second-line anti-leprosy treatment. A pilot study found minocycline effective in eight out of ten recalcitrant ENL patients.⁶⁷ A randomised controlled trial comparing clofazimine and minocycline in chronic and recurrent ENL showed that minocycline provided earlier control, longer remission and fewer side effects, though both groups had similar flare-ups and additional prednisolone requirements.⁶⁸ Colchicine has also been repurposed for ENL.⁶⁹ A network meta-analysis indicated potential efficacy for clofazimine, followed by dapsone+ rifampicin, in treating type 2 leprosy reactions.⁷⁰ However, in practice, immunosuppressants or immunomodulatory agents are often needed for managing severe reactions.

MDT is often restarted to control chronic/recurrent ENL. An alternative regimen with minocycline, clofazimine and ofloxacin may be effective for patients with high bacillary loads and frequent reactions.⁷¹ However, the role of MDT in managing reactions is contentious, with inconsistent efficacy reported.⁷² Immunotherapy, especially *Mycobacterium indicus pranii* (MIP), has shown promise in preventing and controlling ENL episodes.^{73–75} Gupta *et al.* reported a patient with ENL refractory to multiple treatments who responded well to a single dose of MIP vaccine, though rare exacerbations have been noted.^{76,77} High-quality data is limited, making

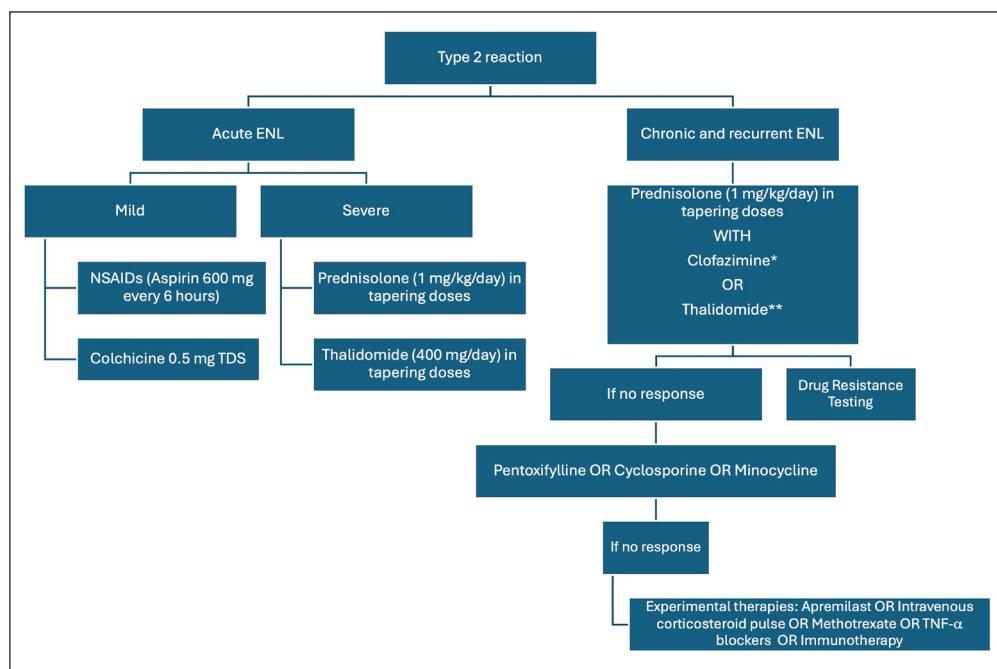


Figure 5: Management of type 2 leprosy reactions (ENL: erythema nodosum leprosum, NSAIDs: non-steroidal anti-inflammatory drugs; TNF- α : tumour necrosis factor alpha). *Clofazimine in a dose of 100 mg TDS for 12 weeks, 100 mg BD for 12 weeks and 100 mg OD for 12–24 weeks. **Thalidomide up to a dose of 400 mg/day in tapering doses, ^aConsider combination with proton pump inhibitors to mitigate associated gastrointestinal adverse effects

conclusive recommendations difficult. An individualised approach, such as MIP or second-line therapies, may benefit those with high bacillary loads and poor responses to MDT. Apremilast, minocycline and colchicine are useful for ENL patients with co-infections or corticosteroid dependence. IL-17 and IL-6 blockers, metformin and SSRIs are potential therapies awaiting clinical studies. Table 4 summarises the current evidence on newer ENL therapies.

Another recent aspect in management of patients with chronic recalcitrant ENL, especially in cases of diffuse LL, is the presence of *M. lepromatosis* infection. These patients most often present with necrotic lesions which resemble the Lucio phenomenon. Hemi-nested PCR targeting 16S rRNA gene specific for *M. lepromatosis* can be utilised for diagnosis. Further studies are needed to elucidate the therapeutic implications of the diagnosis of *M lepromatosis*.⁷⁸

Recent studies highlight the role of resistance in type 1 and 2 lepra reactions and the need for modulation of the treatment accordingly.⁷² Narang *et al.* suggest testing for resistance in all cases of refractory chronic/recurrent ENL.⁷⁹

Prevention

Reactions result from abrupt immune fluctuations, making immunotherapy crucial for managing the immune milieu. Most studies support immunotherapy's preventive role in reactions. *Bacillus Calmette–Guérin* (BCG) vaccine was first reported to be efficacious in leprosy in 1939, where lepromin conversion was noted in 90% of healthy children after receiving BCG. The incidence of reactions and hence

the disability and neuritis were found to be significantly lower in vaccinated patients.⁸⁰ A study comparing the effect of addition of BCG or MIP compared to placebo showed least incidence of T2R in the BCG arm.⁷⁵ However, Shetty *et al.* found no notable response in bacterial or granuloma clearance after administering BCG post-MDT.⁸¹ Despite higher reaction rates with BCG, nerve function impairment was lower.

Mw, now renamed as MIP, is a rapidly growing, non-pathogenic mycobacterium developed by Talwar *et al.* Immunisation with MIP every three months in combination with MDT led to faster clinical improvement, faster bacillary clearance and shortened duration of MDT.^{82,83} A double-blind trial showed higher early phase reactions with MIP due to its immunomodulatory action, but reduced reactions overall after six months, lowering morbidity.⁸⁴ Paradoxical induction of four ENL episodes recurring with each three-monthly dose of MIP vaccine was recently reported in a patient with histoid leprosy.⁷⁷

Incorporating MIP vaccination into India's national program is cost-effective, with an incremental cost-effectiveness ratio (ICER) of ₹73,790 per Quality-Adjusted Life Year (QALY) gained by vaccinating both new cases and their contacts over five years.⁸⁵ A trial comparing MIP and BCG efficacy showed one type 2 and one mild T1R among 14 MIP patients, while five out of ten BCG patients had ENL, with four requiring corticosteroids.⁸⁶

LepVax, a hybrid recombinant vaccine with cross-linked antigens in a Glucopyranosyl Lipid Adjuvant in Stable

Table 4: Summary of newer therapeutics for the management of erythema nodosum leprosum

Medication name	Indication (no. of patients)	Mechanism of action in ENL	Dosage schedule	Efficacy	Adverse effects
Methotrexate ⁵⁹	Recurrent ENL (n=15)	Increased adenosine production, reduction of pro-inflammatory cytokines and increase in anti-inflammatory cytokines	7.5–20 mg weekly (median 15 mg) in combination with corticosteroids	Improvement in reactional symptoms in all reported cases	No serious adverse effects reported in any of the case reports
Cyclosporine ⁴⁹	Acute ENL (n=13)	Inhibits IL-2 production by inhibiting calcineurin, decreased T-cell proliferation	7.5 mg/kg/day in combination with prednisolone, tapered to 2 mg/kg/day in 16 weeks	1.29 recurrences per patient in 32 weeks, mean time to first recurrence was 23 weeks	Hypertrichosis, gum hyperplasia, hypertension
	Chronic ENL (n=20)			2.3 recurrences per patient in 32 weeks, mean time to first recurrence was 7.1 weeks	
Minocycline ⁶⁸	Chronic and recurrent ENL (n=30)	Anti-inflammatory, inhibition of neutrophil chemotaxis and downregulation of pro-inflammatory cytokines	100 mg once a day for three months	Initial control of reaction in 2.97 ± 1.9 weeks, flares in 55.2% patients during follow-up of nine months	Blue gray pigmentation, pain abdomen/epigastric pain
Apremilast ⁶⁵	Chronic or recurrent ENL (n=12)	Structure homology with thalidomide, PDE-4 inhibition, depletion of pro-inflammatory cytokines	30 mg twice daily for six months (after initial standard dose titration) in combination with oral corticosteroids	Resolution of symptoms and signs in 15.63 ± 6.36 days, recurrence of ENL after stoppage of steroids in 27.2% patients	Gastrointestinal adverse effects, urticaria
TNF-α inhibitors (infliximab and etanercept) ⁶³	Refractory ENL (n=5)	Disruption of pro-inflammatory cascade by blockade of TNF-α	Infliximab: 5 mg/kg IV at day zero, repeated at two and six weeks Etanercept: 50 mg/week subcutaneously (case reports of use for up to 12 months)	Rapid improvement in all patients as early as 48 hours	None reported

ENL: Erythema nodosum leprosum, IL: Interleukin, PDE-4: Phosphodiesterase-4, TNF-α: Tumour necrosis factor-alpha

Emulsion (GLA-SE) emulsion, reduced sensory nerve damage and delayed motor nerve damage in armadillos.⁸⁷ Unlike BCG, LepVax did not induce nerve injury in experimental leprosy models. It has shown safety and immunogenicity in a phase 1 trial in healthy adults, but its role as immunotherapy needs further exploration.⁸⁸

Challenges and future directions

The management of leprosy reactions presents significant challenges, particularly with the rising incidence of chronic or recurrent reactions and the emergence of recalcitrant cases. There is a pressing need for biomarkers capable of predicting the disease course and guiding treatment decisions, addressing the imperative for personalised therapeutic approaches in reaction management. Further, the integration of prevention strategies in management of leprosy cases, especially the ones with reactional episodes, cannot be emphasised enough.

Conclusion

Leprosy continues to be an enigma, with several gaps in our knowledge regarding the pathogenesis of leprosy reactions. Lack of representative animal models and sudden onset of reactions make it difficult to evaluate the disease pathophysiology. Reliable biomarkers that may be measured longitudinally to monitor treatment response are being explored. Several therapies are currently undergoing trials for leprosy reactions. As the pathogenesis of disease

continues to be unravelled, targeted therapies may be the future for safe and effective management of this debilitating and stigmatising infection.

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