

# Leprosy Patients with COVID-19: The Double Trouble?

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**Abstract:** *Type 2 leprosy reaction or Erythema nodosum leprosum in conjunction with COVID-19 poses a higher risk for patients with a long course of corticosteroids for its control. Despite regular uptake of corticosteroids, the benefits will usually outweigh the small increase in acquiring SARS-CoV-2 infection. In addition, the actual consequences of M. leprae-SARS-CoV-2 co-infection must be thoroughly investigated. Further detailed work should be done to unleash the factors associated with COVID-19 and their possible correlation with leprosy patients.*

**Keywords:** Leprosy, COVID-19, Erythema nodosum leprosum, Type-2 leprosy reaction, corticosteroids

## 1. Introduction

A hundred years ago, there was a dilemma that circles around leprosy, was it hereditary, or the hypothesis proposed by Armauer Hansen is considered true? These arguments had vital and very different public health consequences(1). At that time there were no effective antibiotics for treating leprosy. However, advancements in sequencing technologies enable researchers to study deeper into its causative organism, *Mycobacterium leprae*, and propose appropriate treatment interventions. In the recent past, fast pace research has been going on to address the challenge of drug resistance *Mycobacterium* species. With the emergence of SARS-CoV-2 from Wuhan city, China in December 2019, several organizations including the Brazilian Leprosy Society warned about the possible impact of COVID-19 on leprosy patients. Leprosy, a granulomatous disease, has severe immunological complications associated with it called leprosy reactions which are characterized by cytokine storm and are the plausible reason for peripheral nerve damage. Patients with Type-2 leprosy reactions or ENL (Erythema nodosum leprosum) show similar types of symptoms to COVID-19 including, high serum NET (neutrophil extracellular trap) marker and altered NLR (neutrophil-to-lymphocyte ratio) (2, 3). Co-infections with other bacteria and viruses have been already reported in patients with leprosy reactions (4). Thus, COVID-19 infection in leprosy patients reveals vital questions about its occurrence and severity of leprosy reactions.

### The Global Leprosy Burden

The primary mandate of World Health Organization (WHO) global leprosy strategies is to reduce the disease prevalence in countries globally. These strategies focus on breaking the chain of transmission and active case detection in high as well as low burden countries. The number of new cases detected during the pandemic period (end of 2020) was highest in South-East Asia with 84,818 cases reported (5). Also, the number of new cases of leprosy detected stands at 8629 among children (5). The decrease in the leprosy cases during the pandemic may be attributed to a disruption in the leprosy programs caused by the cessation of community-based activities, active case detection, stock-outs of essential

drugs at national and local-facility levels, delay in monitoring and detection of nerve impairment.

### Challenges to Leprosy patients

The leprosy patients on prolonged treatment with varying doses of corticosteroids should be considered immunosuppressed and therefore, are more prone to any infection(6). A meta-analysis of a cohort of patients with COVID-19 shows high mortality upon treatment with corticosteroids than the patients who were not treated with it(7). Patients with borderline lepromatous or lepromatous leprosy may have high levels of lactate dehydrogenase isoenzymes (LDH) and may develop neutrophilia during Type-2 leprosy reaction and thus they are more prone to severe COVID-19 infection(8). Also, the lockdown imposed by governments of different countries to contain the spread of SARS-CoV constraints and limit the access to multidrug therapy (MDT) and other essential services. Poverty is another factor that makes the situation worse as the majority of the people suffering from leprosy belong to the overcrowded lower socio-economic group and maintaining social distancing is practically tedious. Social exclusion also increases social inequalities, poverty, and other vulnerabilities. There is a suspected relationship between leprosy and poverty; however, it is difficult to unleash the true correlation at the national and regional levels(1).

## 2. Discussion

### Do corticosteroids exacerbate severity in leprosy patients?

As reported in a previous study, continued uptake of corticosteroids renders a person vulnerable to other infections(6). A recent study concludes that patients with Type-2 leprosy reaction may have natural protection against severe COVID-19 infection due to an increase in interferon-gamma (IFN- $\gamma$ ) levels which is the primary mediator in Type-2 leprosy reactions(9). This study suggests Methotrexate be the safe immunosuppressive agent which may be administered owing to its non-inhibition of host immune response. Another study suggests the early start of steroids to control severe skin manifestations and prevent nerve damage. This study demonstrates Methotrexate to be an ineffective steroid-sparing agent and recommends its uptake

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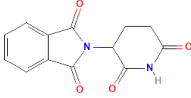
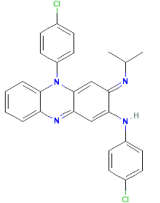
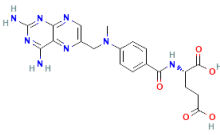
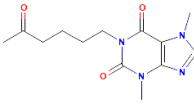
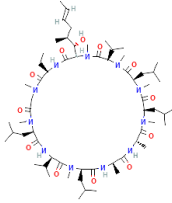
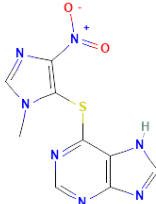
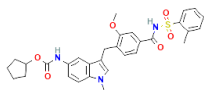
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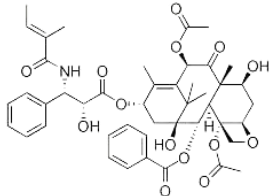
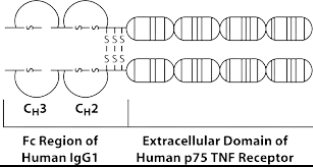
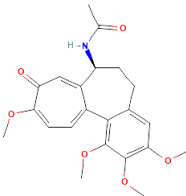
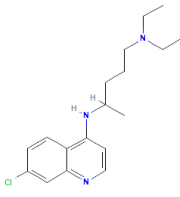
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in ENL patients (9, 10). Owing to their socio-economic conditions, leprosy patients have more frequent contact with SARS-CoV-2 infected patients but continual use of

corticosteroids does not affect the occurrence or severity of COVID-19(11).

**Table 1:** Corticosteroids/drugs used in the treatment of patients with Type-2 leprosy reactions.

Corticosteroid/Drug	PubChem CID	Structure	Reference
Thalidomide	5426		(12)
Clofazimine	2794		(13)
Methotrexate	126941		(9, 10, 14, 15)
Pentoxifylline	4740		(16)
Cyclosporin A	5284373		(17)
Azathioprine	2265		(18, 19)
Zafirlukast	5717		(20)

Infliximab	17396768		(19)
Etanercept	7847807		(21)
Colchicine	6167		(19)
Chloroquine	2719		(15)
Oral zinc	23994	Zn	(19)

ENL is a condition characterized by the presence of neutrophils in skin lesions(2). The commonality among the patients with ENL and COVID-19 is the presence of neutrophilia and high NLR(22). One study showed the presence of circulating and skin-lesion neutrophil releasing NET along with higher DNA-histone serum levels upon comparison with non-reactive multibacillary controls (23). From a clinical perspective, COVID-19 and ENL differ, however, their transcriptome profiling and neutrophil activation are similar. It seems that leprosy/SARS-CoV-2 co-infection may promote the neutrophil activation leading to ENL which causes neurological damage and disability. Thus, evolving knowledge regarding COVID-19 should be carefully applied to ENL patients for their benefit and the greater good.

### The Way Forward

COVID-19 and ENL have marked differences though their transcriptome profiles and neutrophilic activation are similar. Leprosy/COVID-19 co-infection probably triggers the onset of ENL by the destruction of peripheral nerves leading to physical disabilities. Till now, there is no such study that can illustrate the incidence, severity, or recurrence of ENL cases after the insurgence of COVID-19. Further investigations are necessary to establish a clear association regarding the role of neutrophils in ENL and COVID-19. Recent advances in therapeutics lead to more sophisticated drugs for the treatment of COVID-19 but their usability for ENL patients must be ascertained. Several studies have shown the efficiency of corticosteroids in ENL and COVID-19 patients but their possible adverse effects and suitability for an effective alternate class of drugs must be further explored.

In general, COVID-19 disrupted the normal health services across the globe. However, it provided a means to strengthen the digital healthcare ecosystem and initiatives for referral, diagnosis, monitoring, and training staff in countries. Optimization of existing tools such as active case detection, development of new diagnostic tests, and treatment regimens are necessary to achieve a reduction in new cases. Countries have made commendable advances despite the pandemic in achieving the global leprosy strategy 2016-2020 and are committed to ensuring the elimination of leprosy by 2030.

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