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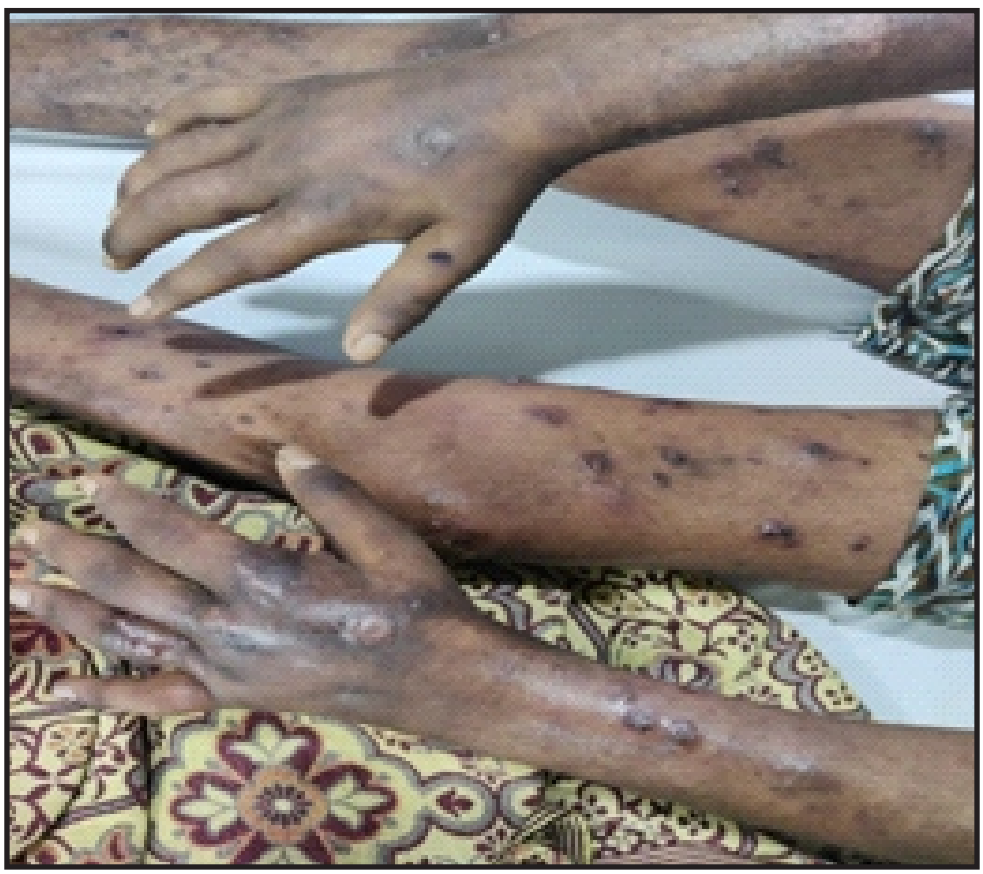

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EDITORIAL

Leprosy & Youth

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For the umpteenth time we have heard our elder generation of leprosy scientists, physicians and researchers expressing their despair about vanishing expertise and decline interest among young researchers and physicians in particular. There is a worry about who will carry on 'Research work' or who shall be the flag bearer of leprosy research in future?!

Oommen C. Kurian dissected precisely in his publication in observer research foundation about unwillingness of the government doctors taking up posting in leprosy division and declining interest & participation of dermatologists. He also highlighted, waning interest among young researchers in the field of leprosy.

There is a need to conduct a nation wide survey among post-graduates aspiring to be a dermatologist or are in the dermatology residency program about how many of them see 'field of leprosy' as a career option. This will give us an insight about the thinking of the young individuals and their commitment about leprosy.

Contribution of IADVL towards leprosy research:

As an IADVL Research Grant Co-ordinator for the year 2020 & 2021, it is a heartening fact about the number of research projects received for the IADVL & IADVL Glowderma Research Grant studies. More so this year(2021) there are 5 projects related to the field of leprosy which have been awarded the grant based on rigorous and blinded jury process. This shows a great commitment and openness on behalf of a private organization to support the cause of the leprosy. Average age of researchers who had applied for these projects was between 35-40 which shows evidence to the contrary belief that young dermatologists are not inclined towards leprosy research. Simultaneously number of conference posters, oral presentations in the subject of leprosy received for national level conferences are significantly high which shows extensive teaching occurring in medical colleges and interest of the post-graduates to show case their research and interesting cases.

Contribution and composition of SIG IADVL Leprosy:

Special Interest Group (SIG) leprosy is a part of IADVL Academy and is constituted by dermatologists with active interest in the field of leprosy. Selection criteria for this is academic and social work carried out in the field of leprosy. Here also if we see average age of members of IADVL SIG Leprosy in past 4 years (2017 onwards) is less than 40. Of the total 10 SIG Members every year more than 50% are below the age of 40 & they work under the guidance of senior co-ordinator of the group.

Social media & New Age India:

With the advent and spread of social media like facebook & Twitter; Leprosy affected people, NGOs, Leprosy scientists are disseminating educative material to fight of the stigma related to the disease and one can also come across various funding opportunities for leprosy related research which are available online. Also, evident is the approach of our young nation to take on all the challenges head on and with this renewed approach, youth is actively fighting the old demons in the mind of elder generation to have an inclusive society for leprosy affected individual.

Promising Future :

Leprosy researchers and followers that with the change occurring in government mindset which is now open and receptive towards IADVL and it's suggestions. Also, change in guard at Indian Association of Leprology (IAL) has instilled life in the association which has been the oldest of its kind. All these things put together and genuine interest among young dermatologists for the cause of leprosy promises a better future and a renewed zeal that we will eradicate leprosy.

HANSENS TRIAL FOR LACK OF CONSENT

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When medical history is chronicled we notice the trials and tribulations, liberties and sacrifices undertaken by past workers to shape the present day glory of 'modern medicine'.

One such episode happened with our revered discoverer of leprosy bacillus, Gerhard Armauer Henrik Hansen.

BACKGROUND

This is circa 1879, precisely the 3rd of November 1879. By this time Hansen was established at the leprosy hospital in Bergen and had also become the chief medical officer for leprosy in Norway. Although he had a personal conviction regarding the infectious nature of leprosy but he could not establish this through scientific evidence. Mind you, those were early days in the times of 'the germ theory of disease', and leprosy was firmly believed to be 'hereditary' and a 'curse of god'. The Koch's postulates (or should I say Henle's idea….) were gaining popularity and this to Hansen meant that if leprosy was indeed caused by an infectious agent, then (a) agent needs to be isolated from each case, (b) it should be cultivable and (c) it must be capable of inducing the disease on inoculation. Hansen had attempted to address the third condition and failed in inducing the disease into animals, as others before him. So, the circumstances became compelling purely out of scientific desperation.

THE INCIDENT

The chief protagonists of this incident are 2, Hansen and a 33 years old 'girl' (Kari Nielsdatter Spidsoen) who had been at the leprosy hospital at Bergen since she was 16. Even prior to this incident the relationship between Hansen and his leprosy patients was cold to say the least, partly because of his insistence of the need for Isolation of lepers and partly due to his refrain that for leprosy 'one was oneself to blame'.

One day after the rounds, this girl was requested by Hansen to accompany him to his office. Without communication of the cause, the girl became anxious and burst into tears at the entrance itself. She was assuaged and asked to come up to a table. Hansen lifted a sharp instrument and took it towards the eye of the patient, at which she naturally lifted her hand in defense. Seeing this, the medical superintendent who was present in the room calmed her down and made her to sit down on a chair. Hansen went ahead and using the instrument pricked her twice in the eye. It is now understood that the girl probably suffered from borderline leprosy and Hansen was attempting to inoculate her assumed insensitive conjunctiva

with material from a leprous nodule of a different patient using the instrument; a cataract knife. Quite naturally, the girl complained that the procedure was painful and that the pain did not go away for weeks after the incident. Needless to say there was a furore in the hospital. On knowledge, Gronvold the pastor first reported the matter to supervisory board which interrogated the protagonists and finally referred the matter to the ministry of justice. There was an inquiry and subsequently the matter went to court.

THE CASE

The chief magistrate in Bergen opened the case with the comment that Hansen had operated upon the patient without her consent and against her wishes. It was further noted that the patient had to suffer significant anxiety and not 'inconsiderable pain'. And it mentioned that Hansen had an intention of inflicting 'a more malignant' form of leprosy than she already suffered. Now, the opinion of the city medical officer, Bidenkap and the director of public health was asked for. At that point of time leprosy was a health problem of concern for Norway and science was no close to treatment as the cause of disease was still to be ascertained. Both the learned men agreed that since the underlying intention of Hansen was to discover the cause of leprosy and this was a question of great importance, the court should proceed to grant no severe a punishment than reprimand. The ministry prepared 2 draft proposals of royal decree. In the first, Hansen was to be convicted under the provisions of chapters 24 and 27 of the 'current criminal code', with imposition of the penalty of loss of office. The second draft was a little complex, herein it was proposed that the present arrangement of Hansen's appointment both as chief medical officer for leprosy and a doctor at the leprosy hospital of Bergen, was to be abolished. This was based on the belief that Hansen had erred in his capacity as a doctor in the hospital and not as a chief medical officer for leprosy. The government adopted both the proposals by a royal decree issued on 17th April 1880. The actual court case, lasted a mere 4 hours. And on 31st May 1880 the verdict was delivered.

THE DECISION

The court found that Hansen had indeed without a just cause, done the girl an injury. He had intentionally failed to take either her consent or informed her of the experiments' purpose. The court took note of the fact that although the pain was 'not inconsiderable', it still was made out to be much more than it actually was by the girl. Interestingly, out of Hansen's own admission the court concluded that he took 'advantage of his position' and wilfully omitted the obligation of informing details of the procedure. The court passed the sentence that Hansen will forfeit his appointment as doctor at the leprosy hospital, although considering his forthcoming conduct during inquiry he had not rendered himself unfit to function as chief medical officer for leprosy. He was fined 90 kroner, the costs of the case.

SOME SCIENTIFIC CONSTERNATION

At that point of time, the case generated a lot of buzz. The scientific community took it as something akin to cocking a snook at them. From accounts it can be made out that what Hansen did was neither exceptional nor disturbingly novel. Infact, in his defence he quoted how his superior Danielssen inoculated himself and a few hospital staff with a similar material. Although on careful dissection of that incident, one can notice the nuanced difference of consent, between these episodes. Nonetheless this case established that no one let alone a 'celebrated scientist', was above law. Thus, in the annals of medical ethics this must have been among the first cases where the sacrosanct 'all empowered' position of the healer was correctly challenged. We should be proud as practitioners of the art of modern medicine, as it had begun to introspect much earlier around 1830 wherein Wilcock in his book 'Laws relating to the medical profession' discussed the need for consent. All concerns on investigations and trials on human subjects were finally put to rest in 1965 when the landmark declaration of Helsinki was codified. This case shall remain one of the earliest harbingers of humane practices while investigating disease and the diseased.

After the case, Hansen went on to become the celebrated discoverer of the 'leprosy bacillus', while no description of Kari can be traced. Tragic but true.

The article has utilized the following articles in preparing this piece, and would like to acknowledge their liberal contribution.

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MOTHER TERESA'S TOUCH TO DIGNIFY LEPERS

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All of us have heard, but only few have truly understood the enigma popularly known as Mother Teresa, often referred to as the most admired person of 20th century or the *Saint of Gutters.* Though she never sought recognition, she exercised an enormous influence over people all over the world. She was born as Agnes Gonxha- Bojaxhiu on 26 the August, 1910 in a sleepy little town of Skopje, Albania. She found her calling to serve the God and the poor at the tender age of 12 and left her family forever at 18 years to join the Loreto Sisters. She was sent to Calcutta, India to begin her training as nun, little did she know that this city would become her home for the rest of her life. She initially served as a teacher for the underprivileged, but moved by the plight of poor, homeless, orphans and dying people on the streets, she requested to leave the order and work with the poor. In 1950, she established her own order Missionary of Charity after permission from the Vatican, and slowly worked towards providing dignity to the poorest of poor whom everyone else had shunned. She soon became a well-recognized figure on the streets of Calcutta and worked endlessly for the downtrodden people.

As we know, leprosy has always been a challenge not only for medical reasons but for social reasons as well because of the stigma it ensues. Mother Teresa's work with leprosy began around 1956 when the sisters realized the growing population of lepers on the streets of Calcutta. Mother Teresa first introduced a mobile dispensary to help these people receive treatment, but soon realized the overwhelming magnitude of the problem. Earlier, Gobra Hospital housed the leprosy cases in Calcutta, but as a result of its closure owing to lack of resources and pressure from the developers, the patients found it difficult to communicate to the new facility which opened on the outskirts of city. Ignorance about leprosy was widely prevalent which compounded by the stigma, made people hostile towards these patients and strongly resisted opening of any clinic in the assessable parts of the city. Even travel on public transport was not allowed for the lepers. On many occasions when mother Teresa went to inspect a potential site of the clinic, she was met with resistance and sometimes was subjected to even stone pelting from the nearby residents. But it never dampened her spirit to serve this neglected section of the society

In those days, dapsone monotherapy was the only treatment for leprosy and had to be taken for a long time. Denial and fear of the stigma often lead to seeking treatment at a late stage which caused increased prevalence of deformities in patients. Fear of contamination by a leper was so much that they were banished from households and even after recovery from the disease, found it hard to obtain any sort of residence or employment. Most of these patients then sought refuge in slums or outskirts of the city and died due to neglect and contempt from their own kin.

As it was difficult to provide care and treatment to such a large number of people, the sisters at the charity often found themselves in scarcity of resources and manpower. Help came to Mother in form of Dr Sen who was a trained skin

specialist and happily offered his services free of charge, for the treatment of the leprosy patients. Slowly over time, eight treatment stations were established all over Calcutta. With the help of the donations, they also started a mobile clinic in a bright blue ambulance which became a symbol of comfort to more than 30,000 leprosy afflicted patients in Calcutta. In years to come, these bright blue mobile clinics would help many untreated Leprosy patients come forward to obtain treatment and these blue vans became easily recognized vehicles on the busy Calcutta roads.

In the initial years the sisters of Missionary of Charity worked on betterment of Titlagrah also, which was a makeshift cluster of huts on the outskirts of Calcutta serving as the final heaven for the destitute lepers. These people found it difficult to travel to the city for treatment and were ignored by the local clinics also. A small clinic was first established near the railway sheds but as it could not cope with the increasing burden of the patients, Mother sought financial help with the famous slogan *"Touch the leper with compassion"*. Donations poured in and a permanent facility was built up in Titlagrah consisting of a hospital, a cafeteria and a rehabilitation center in 1959. Over the next 10 years other buildings were added which included a school for the children of leper patients as well as childhood lepers. Moved by her diligent work towards lepers, the government of India gifted mother Teresa 34 acres of land located near Asansol in 1961 and a token amount of one rupee per year was to be paid by the Missionary of Charity. This jungle like area was converted in to the most famous project of Mother Teresa for leprosy patients, *SHANTINAGAR*- The place of peace for lepers. Though funds for the infrastructure were raised by people everywhere including foreign nations, still building the facility was an uphill task. When the condition was looking bleak, unexpected guidance and financial help came from the Pope Paul VI. Deeply touched by work of the charity in Nirmal Hriday (a home for dying established at Kalighat) he gave them the limited-edition car which was gifted to him by the American Catholics. As there was no practical use of the car to the sisters, Mother Teresa sold it in a raffle and raised 460000 rupees! This money was then used for starting the construction of facility at Shantinagar which began in 1968 and slowly over the years cottages of lepers, rehabilitation center, vegetable and fruit gardens and a hospital were built up. Around 400 lepers and their family were offered a place which they could call home and not face discrimination. They were made self-sufficient by growing their own vegetables/fruit/rice, learning to make bricks to build cottages for new arrivals, tending to their cattle and weaving their own clothes. Even today the trademark white saree with three blue stripes worn by the sisters in MOC are woven by the leprosy patients at the centers set up near Titlagrah and Shantinagar. The Shantinagar township still serves as a leper colony and provides rehabilitation and dignity to the social outcast leprosy patients.

When MDT became available in the 1980, Mother Teresa took it upon herself to spread awareness about the drugs amongst patients as well as medical professionals.

Though the motto of Mother Teresa's charity work was "Do small things with great love", these "small things" done by her selflessly, left a life changing impact on the lepers and their families.

MENTAL HEALTH IN LEPROSY – A NEGLECTED ISSUE

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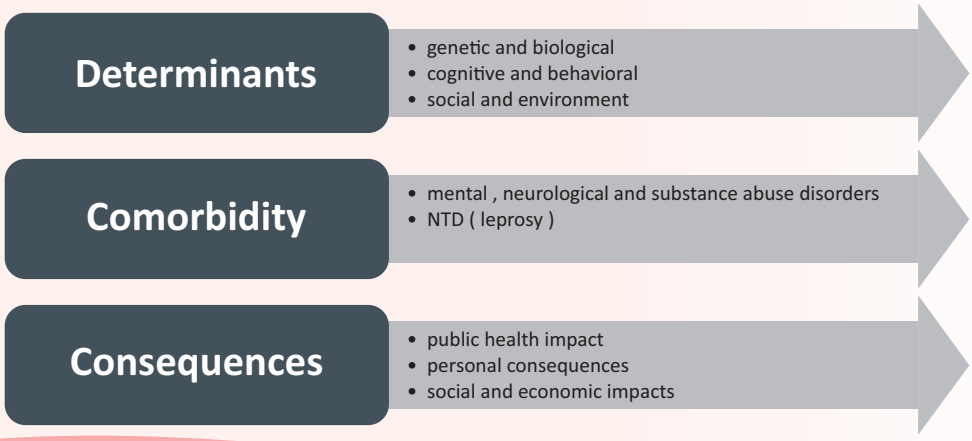
Disabilities and secondary impairments in leprosy result in physical and psychological consequences like activity limitations, economic and physical dependence, social exclusion and stigma. All these factors are correlated and can worsen the mental wellbeing of the leprosy-affected persons[1]. The WHO Global Leprosy Strategy 2021-2030[2] lays down the long-term vision of 'zero leprosy' by extending a gamut of services which includes not only treatment with drugs and rehabilitation but also addresses the mental health issues associated with the disease. On World leprosy day 2021, WHO invited the international community to unite around one goal, which is to Beat Leprosy and help spread the word that Leprosy Is Curable, join in the fight to End Stigma, and advocate for the Mental Wellbeing of persons who have experienced leprosy and other neglected tropical diseases.

Association of leprosy and mental health

Individuals and communities affected by leprosy may well represent one of the highest risk populations for mental disorder[3]. Diagnosis with leprosy can be distressing. If the diagnosis results in social exclusion and rejection, this may lead to mental health problems such as emotional stress, anxiety, depression, isolation and even suicide attempts.

Psychological distress among leprosy patients has been shown to be significant [4,5], the prevalence ranging from 12.5% to 76% [6]. Depression(71%) is the most frequently identified psychiatric condition [7,8] followed by anxiety disorders (10% to 20%)[6]. Suicide attempts and suicidal thoughts among leprosy patients[9] have also been reported. Other conditions linked to leprosy are sleep disorder, dementia, hysteria, epilepsy, paranoid and psychotic state, delusional , hypochondriacal , adjustment , substance related disorders, somatic symptom disorder and hyperactivity disorder[6,9,10,11,12]. Other negative feelings and attitudes that can affect mental wellbeing are those of fear [13], fear of rejection, isolation, stigmatisation and prejudice. They are shamed due to physical disfigurements that results in stigmatisation [14], low self-esteem and lack of confidence[5].

Figure 1: *Shared determinants, comorbid conditions, and consequences of mental health conditions and NTDs (adapted from Mental health of people with neglected tropical diseases)* [15]



Mental health, a neglected domain

Mental health in India has been long neglected. People with NTDs often face stigma, discrimination and social exclusion, which prevent help seeking, access to treatment or adherence to it. Personal level discrimination occurs in communities, such as fewer marriage prospects, job loss, fewer income opportunities or direct abuse. Economic loss occurs in the form of loss of jobs and cost to care. Integrated chronic and psychological care is not a focus of leprosy programmes at present and few mental health intervention studies have been conducted in leprosy and chronic leprosy sequelae [16].Only about 1.3% of its annual health budget is spent on mental health. Treatment gap for mental disorders in India is about 85% for common mental disorders. There is gross inadequacy and inequity in terms of availability of mental health resource personnel and health facilities that could provide appropriate care at different levels[17]

Interventions to address mental health conditions

For leprosy to be defeated we need to identify and address the mental health problems of people. Integrating mental and physical healthcare services for individuals living with chronic conditions is the way forward [1819]. With Ayushman Bharat program through Health and Wellness Centres , we hope that the barriers and gaps to mental health care will be addressed and overcome. A stepped care approach [18] in stigma and group counselling interventions have been proven suitable administration by no specialists[20] , supporting similar research findings in the global mental health community[21].

Everyone has a role to play in bringing mental health services to those who need it most – policy makers, service providers, civil society, and people with lived experience of mental health conditions and psychosocial disabilities[22]. Interpersonal level intervention can focus on positive social contact and increasing support and care in the person's environment. At the Community level stigmatizing and discriminatory attitudes and behaviours must be reduced. Training and person-centred institutional policies need to be implemented at the organization level where pharmacological management of mental, neurological and substance use disorders may be provided by trained primary health care professionals. Health service providers can use integrated psychosocial, pharmacological, and educational approaches to address the mental health burden associated with NTDs. At the government level, policy changes can be advocated for discriminatory or stigma enforcing laws, strategies and campaigns rolled out to increase understanding of mental health and behaviour.

Those at the highest risk of significant psychological impact will require more resources. In such settings, it may be more suitable to focus resources on leprosy with chronic sequelae and/or high levels of stigmatisation. Thus, a grass roots approach can be an effective way of providing continuity of care for individuals affected by leprosy and disability centred upon peer support and economic empowerment groups [23,24].

Conclusion

Progress in research and partnership in the past few years has seen mental health emerge as a key cross-cutting area of research. Effective psychosocial interventions need to be demonstrated that can be scaled up and integrated into existing programme activities. Success in this process is dependent upon the input of affected communities and those living with irreversible disabilities. Further engagement and knowledge sharing outside of the leprosy community is also critical to drive future collaboration and innovation in this process.

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LEPROSY IN THE ERA OF COVID-19: A NEGLECTED DISEASE!

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The coronavirus infection, which has been affecting the whole world for about 2 years, has caused an increase in many dermatological diseases or changes in their course due to the cytokine storm. COVID-19 infection has also caused delays in the early diagnosis and treatment of chronic diseases such as leprosy.[1] Because cytokine storm develops in leprosy patients, it has been suggested that leprosy reactions and neurological sequelae may be more in case of COVID-19 infection.[2] Risk of COVID-19 infection contamination is expected to be high, as leprosy patients will have less access to disinfectant due to their poor economic situation.[1] In the following period, experiences with the course of leprosy patients with COVID-19 have been reported.[3-7]Contrary to other case reports, Santos *et al*.[3] reported 4 leprosy patients with COVID-19 infection and reported that 4 patients died without a leprosy reaction. This mortality rate (22.2%) is higher than the mortality of COVID-19 infection observed in patients without leprosy. However, the uneventful course of COVID-19 infections in other cases suggested that these deaths may be related to comorbidities. Of the 4 cases who died after infection, one had hypertension, one had diabetes mellitus with hypertension, and one was a smoker.[3] Neutrophils can cause tissue damage by releasing neutrophil extracellular traps (NETosis)[8] which is more commonly seen in patients with systemic manifestations of COVID19, hence the higher mortality rate in study by Santos *et al*[3]despite lack of reactions.[3,8] Modulation of neutrophils activity may be a future hope for lepers co-infected with SARS-CoV-2.[9] It has been found that COVID-19 infection does not increase the leprosy reaction as expected.[6] Type-2 leprosy reaction is observed in 15.4% of patients with lepromatous leprosy.In contrast, type-2 reactions was reported in 1out of 5 leprosy patients who developed COVID-19 co-infection, that was suppressed with thalidomide.[4,6] Type-1 leprosy reaction, characterized by the development of Th1 and Th17 responses against *Mycobacterium leprae* in patients in the tuberculoid leprosy spectrum, was detected in 2 of them and was controlled with systemic corticosteroids.[6] It is sometimes believed that MDT may "unmask" severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of patients[6], however multiple studies have shown that MDT could have protected them from progressive signs of COVID-19 owing to immunomodulatory properties. It should be noted that dapsone therapy can cause eosinophilic pneumonia and methemoglobinemia which can mimic "happy hypoxia" (i.e. low oxygen saturation and absent clinical features of respiratory distress) seen in COVID-19 infection.[10,11] It has been determined that clofazimine treatment has an antiviral effect against coronaviruses, and this has a synergistic effect with remdesivir.[12]Systemic corticosteroids and cyclosporine are used not only in COVID-19 infection but also in the treatment of leprosy reactions. However, due to the reported development of leprosy lesions during treatment with an interleukin 6 inhibitor (tocalizumab),this issue should be taken into account during the treatment of COVID-19 in leprosy endemic areas.[13]COVID-19 infection has shown us once again that vaccines are our most important weapon in the prevention of epidemics. Kamal et al.[14] noted that addition of *Mycobacterium Indicus Pranii* (MIP) vaccine to the standard MDT resulted in lowering incidence of lepra reactions in patients with borderline leprosy who are susceptible to immune shifting with subsequent higher risk of lepra reactions. Incidentally, MIP is also a part of trial for boosting immunity in COVID-19-infected patients (ClinicalTrials.gov).[15] Development of efficacious vaccines against SARS-CoV-2 is very welcome; however,

it is unclear when these will be widely available in many leprosy-endemic settings.[7] Recently, with the help of Indian pharmaceutical companies, such as the Serum Institute of India, Bharat Biotech, and ZydusCadila, a very low-cost COVID-19 vaccine has been produced for local population and other developing countries.[16] Based on these observations, the clinical outcome of leprosy patients co-infected with SARS-coV-2 may be variable. Further studies, that may include *"in vivo*" assessment of the possible co-existence of SARS-CoV-2 and lepra bacilli in the lepra reactions, are needed to explore the "inter-active" affair between the ancient "leprosy" and the "recent" infectious disease "COVID-19". That would restore the fighting against leprosy in the endemic countries, which is negatively impacted by the COVID-19 pandemic, to its norm.

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COMMENTARY ON EMERGING DRUG RESISTANCE SCENARIO IN LEPROSY

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The first successful chemotherapy using promin for leprosy was reported in 1948 at a leprosarium in Carville, Louisiana, USA. Promin was replaced by a more effective sulfone, dapsone after 6 years. Within few decades' resistance was observed among patients due to inappropriate monotherapy. Due to resistance high relapse rate was observed and in these cases resistance to dapsone was observed. It is known as secondary resistance (resistance is observed in already treated cases with that individual drug). These resistant cases could transmit dapsone resistant strains to susceptible persons. It is known as primary resistance (resistance is observed in never treated cases). Then a strategy was developed to combat resistance and WHO introduced MDT in 1982. Due to introduction of MDT for the treatment of leprosy, the decline in the prevalence of leprosy was observed and in 2005 the vertical programme of the National Leprosy Eradication Programme was gradually merged with the general health system in India. At this stage of elimination, there have been reports of relapses from many endemic countries, indicating that these relapses might be due to the emergence of resistant strains of *Mycobacterium leprae*. The emergence of drug resistance is a concern and a threat for many infectious disease intervention programmes, especially those that have secondary prevention (chemotherapy) as the main component of their control strategy. Leprosy caused by multidrug-resistant *Mycobacterium leprae* is an emerging public health concern worldwide. Global efforts to control leprosy by MDT have led to a significant decrease in the number of registered patients. Current recommended control measures for treating leprosy with MDT are designed to prevent the spread of drug-resistant *M. leprae*. However, drug resistance is still observed and research in chemotherapy must continue.

Dapsone is still a fundamental component in MDT. Dapsone is bacteriostatic and it inhibits folic acid synthesis by competitive inhibition. Dapsone is an analogue of p-aminobenzoic acid (PABA) which targets dihydropteroate synthase (DHPS) encoded by *folP1* and it is involved in folic acid synthesis. Another important component of MDT is rifampicin, which was included in MDT in 1970s due to its high bactericidal activity which was shown clinically and experimentally. Rifampicin targets β subunit of RNA polymerase which is encoded by *rpoB*. Binding of rifampicin to β subunit inhibits DNA dependent mRNA transcription. Clofazimine has been proven to be a weakly bactericidal drug against *M. leprae* in mouse

model. The mechanism of action is not fully elucidated but the binding of clofazimine with GC rich domain of mycobacteria is suggested. It is anti-inflammatory. Till now no molecular target is known for drug resistant to clofazimine. Hence, reports on resistance to clofazimine are rare.

As *M. leprae* is non-cultivable we can do drug susceptibility testing by mouse footpad method, mutation detection by PCR-DNA sequencing, mutation detection by DNA micro-array. Recently, rapid drug susceptibility method is evaluated as a screening tool named real time PCR high resolution melting (qPCR-HRM) curve analysis but for confirmation we need to go for PCR-DNA sequencing.

Resistance to dapsone, rifampicin and ofloxacin (used as second line drug) can be detected by molecular techniques. Emergence of drug resistance must lead to the implementation of intervention programme. Keeping an eye on magnitude of the problem is an important way to manage it efficiently. In this context WHO has done sentinel surveillance of drug resistant strains for 10 years from 2008 – 2018 in India, China, Brazil, Myanmar, Vietnam, Philippines, Indonesia, Columbia, Ethiopia and Mali. During this surveillance, mutation to any drug conferring resistance was observed in 8.0% of *M. leprae* strains. Globally rifampicin resistance was observed in 3.8% cases. However, in relapse cases it was 5.1% (secondary resistance) and 2.0% rifampicin resistance was observed in new cases (primary resistance). Dapsone resistance rate was found to be 5.3% (6.8% secondary resistance, 4.0% primary resistance). Ofloxacin resistance rate was found to be 1.3% (1.7% secondary resistance rate and 1.0% primary resistance rate) (Cambau et al, 2018). We started reporting rifampicin resistance from 2014 in TLM hospitals. We observed 3.6% cases which were resistant to rifampicin, 8.1% cases were resistant to Dapsone/ofloxacin (Lavania et al, 2014). Even in 2015 our group reported primary drug resistance to rifampicin in 7 out of 16 new cases of leprosy (Lavania et al, 2015). Further, we reported 2 cases which were resistant to all 3 drugs in 2018 (Lavania et al, 2018). Resistance in all these cases was reported by molecular methods PCR-DNA sequencing method using primers and protocols according to WHO “Guidelines for global surveillance of drug resistance in leprosy”. Rifampicin resistance has not reported only in India, but it has also been reported in China, Brazil and Colombia (Chokkakula et al, 2019; Beltran-Alzate et al, 2016; da Silva Rocha et al, 2012). To manage the resistance cases efficiently the accurate clinical data should be maintained for all the resistant cases and their past treatment history should be traced. Clinicians should be able follow such cases with utmost interest for the benefit of the leprosy control Programme. Further, to overcome the challenge of controlling the disease and to sustain the on-going declining trend of leprosy in endemic countries, it is essential to keep a watch on drug sensitivity patterns in the present settings. To prevent the development of multidrug-resistant strains of *M. leprae*, current leprosy control strategies will be of utmost

importance and would immediately need the establishment of a built-in mechanism of a surveillance for identification of drug resistant strains early along with its immediate treatment.

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MANAGEMENT OF TYPE 2 LEPRA REACTION IN SPECIAL SITUATIONS

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Type 2 lepra reaction (T2LR), also known as Erythema Nodosum Leprosum (ENL) is a severe multisystem immune complex (antigen-antibody reaction) and T cell mediated (Type 3) reaction exclusively seen in lepromatous leprosy patients and rarely in borderline leprosy patients. T2LRs most commonly occur around 5-6 months after starting multi drug therapy (MDT), but may appear ***de novo*** before the diagnosis of lepromatous leprosy or even many years after MDT due to persistence of granular bacilli. A study from Ethiopia (2014) has documented ENL in 34.7% patients at the time of leprosy diagnosis, 39.8% developed ENL during the course of treatment with MDT and 25.5% after successfully completing a 12-month course of MDT. [1]

Immunopathogenesis of Type 2 Lepra reaction:

Activation of T cells seems to be the primary event in the pathogenesis of T2LR secondary to the precipitating factors. It releases cytokines which further activates macrophages leading to proinflammtory response. Release of *M. lepra* antigens (phenolic glycolipid-1 and major cytosolic protein of *M. leprae*) form immune complexes with antibodies and the lipopolysaccharide of *M. leprae* and can also stimulate neutrophils which then release TNF-α and IL-8. [2] The increase in number of IL-2 receptors on the immune competent cells reinforces the role of cell mediated immunity in the pathogenesis of T2LR. [3]

In this paper, we will discuss the management of T2LR in special situations like in pregnancy, in children, HIV infected patients, COVID infection and other immunosuppressed conditions.

Type 2 Lepra reaction in pregnancy and lactation:

Various studies have proved that pregnancy is associated with shift from a Th1 to Th2 response with a reversal in puerperium. Precipitation of T2LR in puerperium could be due to physical stress of parturition and a reverting to normal plasma ACTH and cortisol which were increased during pregnancy, while trigger for ENL in third trimester is increased incidence of infections. [4]

Treatment of T2LR in pregnancy and lactation involves starting or continuing the regular MDT comprising of rifampicin, clofazimine, and dapsone. Multi drug therapy is considered safe for both mother and child during pregnancy and

lactation. [5] Treatment for ENL should be started as soon as diagnosed in pregnancy to prevent further neurological damage. Oral steroids are the mainstay of treatment in pregnancy and lactation for the treatment of ENL. Prednisolone should be used in a tapering regimen with initial dose as 40 mg daily or 1 mg/kg/day and tapering by 10 mg every 2 weeks as follows:

40 mg/day for weeks 1 and 2

30 mg/day for weeks 3 and 4

20 mg/day for weeks 5 and 6

15 mg/day for weeks 7 and 8

10 mg/day for weeks 9 and 10

05 mg/day for weeks 11 and 12.[6]

Maximum dosage of prednisolone is 1 mg/kg of body weight.

Because of the well known teratogenic side-effects, WHO does not support the use of thalidomide for the management of ENL in pregnancy. [6] Other immunosuppressants like methotrexate, cyclosporine and azathioprine are also avoided in pregnancy as risk of hypertension and pre-eclampsia exists with these agents and can cause fetal defects as well as early termination of pregnancy (Table 1). [7,8]

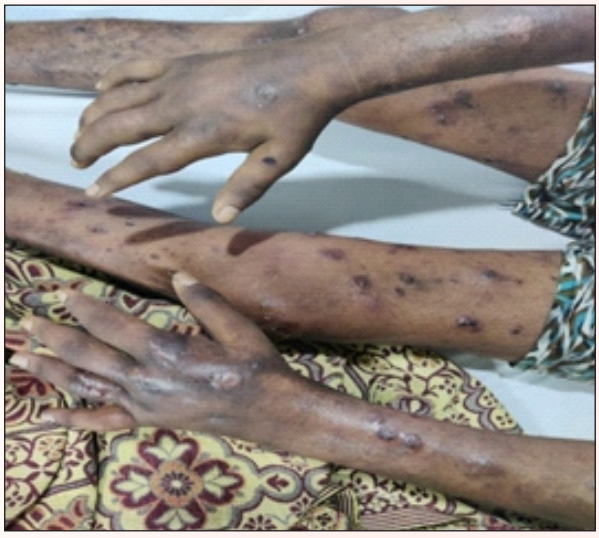
Table 1: Various drugs used in management of ENL in pregnancy and lactation

Antileprosy drugs	
Rifampicin	Generally safe in pregnancy and lactation. It can cross the placenta, however, no increased risk of birth defects have been seen. About 5% of the drug can also be transferred to breast milk but no adverse effects have been reported.
Dapsone	Generally safe in pregnancy and lactation. Can be associated with neonatal hemolysis and methemoglobinaemia when given in 3rd trimester. Supplementary folic acid – recommended
Clofazimine	Safe in pregnancy and lactation. Can cause reversible skin discoloration in the breast-fed child.
Ofloxacin	To be avoided in pregnancy and lactation (risk of arthropathy seen in animal studies).
Minocycline	Teratogenic in pregnancy and not used in lactation due to risk of infant teeth discoloration and damage, secreted in breast milk.

Anti-reaction drugs	
Prednisolone	Can be used. Monitor for adverse effects, especially hypertension and hyperglycemia. Theoretical risk of hormonal disturbances in the fetus. Safe in lactation, but feeding should be deferred until four hours after ingestion of the drug to reduce infant's exposure to peak concentration of steroids secreted in breast milk.
Thalidomide	Teratogenic in pregnancy, so contraindicated.
Immunosuppressants	Cyclosporine, Methotrexate and Azathioprine are contraindicated in pregnancy and lactation.

Type 2 Lepra reaction in children

In childhood leprosy, reactional episodes and disabilities are less frequently seen and if present are more likely in older children, due to their relatively well developed immunity **(Figure 1).**



Lepra reactions are the main causes of neural damage and deformities in children. The focus of treatment of T2LR in children is to prevent deformity and disability. Each patient has to be started/ continued on multibacillary (MB) MDT as per their age and body weight and oral steroids have to be administered (table 2). While deciding the dosing schedule of steroids, the special adverse effects of steroids in children (effects on skeletal growth and puberty) must be taken into consideration, in addition to the general side effects like immunosuppression, hyperglycemia, osteoporosis, and adrenal suppression. Some clinicians also prefer alternate day steroid dosing to reduce adrenal suppression. [9] After explaining the side effect of skin discolouration, clofazimine can also be started in severe ENL. Other immunosuppressants like methotrexate should be considered in difficult to treat cases or patients not responding to oral steroids.

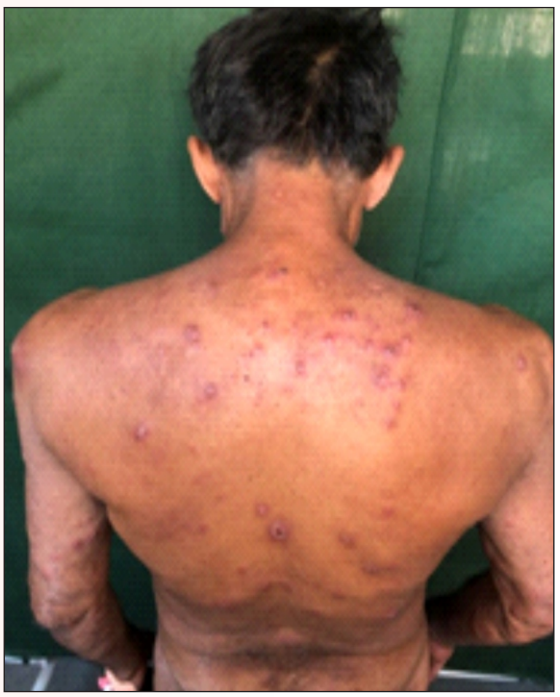
Table 2: Type 2 Lepra Reaction Drugs for children

Oral Steroids	Prednisolone Dose – 1 mg/kg/day For a child of about 30-35 kg body weight, a 12-week course beginning at 30 mg prednisolone per day and tapering in the following manner: 30 mg OD x 7days 25 mg ODx 7days 20 mg OD x 28 days 15 mg OD x 14 days 10 mg OD x 14 days 05 mg OD x 14 days.
Oral Clofazimine	Start with 1.5–2 mg/kg three times daily for one month, then reducing by one dose per day each month. Maximum: 300 mg daily.

Type 2 Lepra reaction in HIV positive patients

Type 2 lepra reactions are reported less frequently in retropositive individuals and it has been suggested that HIV infection may decrease the risk of this complication **(Figure 2)**. [10]

It has been recommended that HIV and leprosy co-infected patients should be treated with standard MDT together with highly active antiretroviral therapy (HAART). [11] For the management of T2LR in HIV positive patients, oral steroids can be used as in an immunocompetent individual. Thalidomide has also been used with success in the management of severe, recurrent ENL, refractory to high doses of daily steroids in patients with coexistent HIV infection. [12] It has also been reported to produce an antiretroviral effect, possibly through inhibiting TNF production and by blocking TNF stimulated HIV replication. [13] Due to these properties, it appears to be the drug of choice for treating ENL in HIV positive leprosy patients. Sachdeva et al have reported an interesting case of refractory T2LR in a HIV infected patient with normal CD4+ counts



which could not be controlled until anti-retroviral therapy was initiated. [14]

Type 2 Lepra reaction in COVID-19 patients

The coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been hypothesized that COVID-19 infection can lead to increased incidence or precipitation of T2LR by inducing an extensive neutrophil infiltration in body tissues as has been evident from autopsies carried out from lung specimen of severe COVID-19 patients. [15] However, preexisting T2LRs could provide natural protection against severe COVID-19 infection, as they are associated with an elevated INF-γ mediated inflammatory response which is important for the clearance of SARS-CoV-2. [16] Further, the use of oral steroids and other immunosuppressants for the management of type 2 reaction in leprosy patients with ENL could have an impact on the course of COVID-19 infection. Risk factors for T2LRs have always included co-infections, thus potentially making COVID-19 a potential trigger.

Following points should be considered for the treatment of a case of T2LR with COVID-19 infection:

1. MB-MDT should be continued. Patient can be given accompanied MDT to reduce the number of hospital visits.
2. The high doses of steroids have shown to precipitate a broad spectrum of bacterial, fungal and viral infections inCOVID-19 patients as well as the increased risk of developing complications. [17] However, the results of an open labelled RECOVERY trial has shown decreased mortality after using dexamethasone in patients receiving oxygen support while no benefit and possible harm in the hospitalized patients without respiratory support. [18] Therefore, in a patient with ENL developing COVID-19, the recommended dose of prednisolone can be started/ continued. Systemic corticosteroids and thalidomide used extensively in type 2 lepra reactions are useful in COVID-19, with observations skewed favouring systemic corticosteroids. [19] If a patient of T2LR develops COVID-19 infection, steroids should never be stopped abruptly.
3. Thalidomide can be used for treatment of severe and resistant ENL in a COVID-19 patient, as it possess antiviral and anti-inflammatory properties. The concomitant use of thalidomide and oral corticosteroids in ENL increase the risk of coagulopathy. In addition, COVID-19 infection may predispose patients to various thrombotic complications. Therefore, it is advisable to start prophylactic antithrombotic therapy and regular monitoring of coagulation profile if the patient is on combination therapy.
4. Colchicine can be tried in the condition of co-existence of COVID-19 and T2LR. [20] Colchicine has proven efficacy in moderate to severe COVID-19 infection as per a recent randomized, double blinded, placebo controlled trial.

[21] So, it should be used as a preferred drug in the management of mild and moderate ENL and COVID-19 coinfection.

5. Clofazimine is a safe and effective option as it has antiviral action too. According to a recent article an in-vitro study demonstrated that administration of clofazimine in a therapeutic or prophylactic manner reduced viral load in the lungs and also faecal viral shedding. [22]
6. Pentoxiphylline has shown additional benefit in COVID-19 pneumonia due to its strong anti-inflammatory effect. [23] It has also been traditionally used in management of T2LR and can be continued in patients already receiving the drug.
7. Hydroxychloroquine does not provide any survival benefit in COVID-19 infection as well as no additional benefit in the management of T2LR. [24] Hence, it is not a preferred drug in T2LR patients with COVID-19 infection.
8. Immunotherapy using *Mycobacterium* w (MIP) vaccine in patients of MB leprosy has been found to decrease the incidence and severity of T2LR in these patients. The rapid fall in the bacteriological index with the use of this vaccine may explain the lower incidence of T2LRs, as well as the occurrence of these reactions, earlier in the course of the disease as compared to the control group.[25] Recently, an exploratory, randomised, double-blind, placebo-controlled trial of hospitalised subjects with severe COVID-19 (pulmonary infiltrates and oxygen saturation ≤94% on room air) was conducted across four tertiary care centres in India, where patients were randomised to receive either MIP intradermally or a matching placebo for three consecutive days. Subjects in the MIP arm had better clinical outcomes than placebo.[26] Based on these observations, MIP vaccine might be a safe and effective therapeutic option for the concomitant infection.
9. Additional therapeutic options for management of lepra reactions along with Covid 19 co-infections are minocycline, apremilast, and TNF alpha inhibitors.

Type 2 Lepra reaction in organ transplant patients:

The management of leprosy in solid organ transplant patients is challenging because of possible drug interactions between rifampicin and cyclosporine which in some cases might lead to fall in cyclosporine levels and hence development of graft rejection. Hence, leprosy in this patient group may require the use of alternative antimycobacterial agents (e.g. minocycline, ofloxacin). Clofazimine is avoided in heart transplant patients due to impaired cardiac conduction associated with it. [27] Oral prednisolone and other immunosuppressants used for preventing graft rejection should be continued which will also help in the treatment of T2LR.

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FROM JOURNAL'S UPDATES

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1. Molecular epidemiology of leprosy: An update

Avanzi C, Singh P, Truman RW, Suffys PN. Molecular epidemiology of leprosy: An update. Infect Genet Evol. 2020 Dec;86:104581. doi: 10.1016/j.meegid.2020.104581. Epub 2020 Oct 4. PMID: 33022427.

Molecular epidemiology investigations are notoriously challenging in the leprosy field mainly because of the inherent characteristics of the disease as well as its yet uncultivated causative agents, *Mycobacterium leprae* and *M. lepromatosis*. This review discusses the advantages and drawbacks of the main tools available for molecular epidemiological investigations of leprosy and summarizes various methods ranging from PCR-based genotyping to genome-typing techniques.

In the pre-genomic era, two VNTR loci were described that showed variability between strains from different countries (rpoT hexamer) or locally (GAA)21. Later, the availability of the complete M. leprae genome allowed identification of an additional 33 microsatellites (repeat units of less than 6 bp) and 11 minisatellites (repeat units of 6 to 100 bp) loci from which a panel of 16 was eventually characterized and validated as discriminatory using clinical isolates (> 500) from six countries. Also comparing the genomes of four *M. leprae* strains from India, Brazil, Thailand and the United States revealed 84 informative markers capable of discriminating 4 SNP-types based on three distinct loci and 16 M. leprae SNP-subtypes 1A-D, 2E-H, 3I-M and 4N-P. Mapping these polymorphisms in more than 400 strains arising from 28 different countries showed that the distribution of SNP-subtypes was correlated with the geographical origin of the patients, and suggested that SNP-typing could be a robust tool for future phylogeographic and evolutionary studies.

2. Factors associated with the development of leprosy in contacts: a systematic review and meta-analysis

Niitsuma ENA, Bueno IC, Arantes EO, Carvalho APM, Xavier Junior GF, Fernandes GDR, Lana FCF. Factors associated with the development of leprosy in contacts: a systematic review and meta-analysis. Rev Bras Epidemiol. 2021 Jun 30;24:e210039. Portuguese, English. doi: 10.1590/1980-549720210039. PMID: 34231829.

Leprosy in contacts of patients involves social determination, individual susceptibility, and difficulties in access to disease control actions, but modifiable risk factors are the main determinants of illness in this population.

The search resulted in 2,148 references and included 24 reports. Most of the studies had been conducted in Brazil and India, had a cohort design and included household, neighbors, and social contacts. The risk factors associated with illness

due to leprosy in contacts were: illiteracy (RR = 1,48; 95%CI 1,22 – 1,79), living in the same house (RR = 2,41; 95%CI 1,87 – 3,10) of a case of leprosy with high bacillary load (RR = 2.40; 95%CI 1.69 – 3.41), seropositivity to the Mycobacterium leprae PGL-1 (phenolic glycolipid-1) antigen (RR = 3.54; 95%CI 2.21 – 5.67), presence of the bacillus in the bloodstream (RR = 10.61; 95%CI 4.74 – 23.77) and negative Mitsuda reaction (RR = 2,68; 95%CI 1,76 – 4,07). Immunization with BCG (bacillus Calmette-Guérin) vaccine had a protective effect against leprosy.

3. Revised estimates of leprosy disability weights for assessing the global burden of disease: A systematic review and individual patient data meta-analysis

Nanjan Chandran SL, Tiwari A, Lustosa AA, Demir B, Bowers B, Albuquerque RGR, Prado RBR, Lambert S, Watanabe H, Haagsma J, Richardus JH. Revised estimates of leprosy disability weights for assessing the global burden of disease: A systematic review and individual patient data meta-analysis. PLoS Negl Trop Dis. 2021 Mar 2;15(3):e0009209. doi: 10.1371/journal.pntd.0009209. PMID: 33651814; PMCID: PMC7954345.

Disability weights form an integral component in the calculation of the burden estimates. However the published global burden of disease estimates for leprosy is considered to be a gross underestimation as the methodology for calculation of the weights focuses only on physical impairment and lacks the perspective of the patient. In this study, authors systematically reviewed the literature and performed an individual patient data meta-analysis for revising the disability weights for leprosy using domain scores from health-related quality of life instruments. They found that the revised weights were considerably higher than the current weights, and were more reflective of the actual disability caused by leprosy. The also found that for individuals without any severe disability due to leprosy (grade0), they still experience comparable suffering.The revised disability weight for grade 2 leprosy disability is four times higher than the published GBD 2017 weights for leprosy and the grade1 the disability weight is nearly twenty times higher. The revised weights for leprosy disability grade 0 are near similar to grade 1 weights, which implies that the leprosy patients without any visible disability also experience comparable suffering. The differences in disability weights compared to GBD 2017 weights are due to the inclusion of mental health status, activity limitation, and pain, among other effects of leprosy as perceived by the patients. The authors recommend revising the health state descriptions for the two leprosy disability grades because the current description excludes activity limitation and participation restriction aspects that are experienced by the patients. The sequelae base of leprosy should be broadened by including leprosy grade 0 disability patients because its revised weight is close to grade 1.

4. Neuropathies of leprosy

Khadilkar SV, Patil SB, Shetty VP. Neuropathies of leprosy. J Neurol Sci. 2021 Jan 15;420:117288. doi: 10.1016/j.jns.2020.117288. Epub 2020 Dec 25. PMID: 33360424.

This review highlighted the different presentation of pure neuritic Hansen disease.The authors recommended that in routine clinical practice, the diagnosis of leprous neuropathy is suspected by an alert physician. The common presentation of nerve involvement in leprosy are mononeuropathy, mono neuritis multiplex, thickened nerves, non healing ulcers, cranial and limb neuropathies, trophic changes and deformities, loss of temperature with preservation of proprioception and tendon reflexs. The uncommon presentation are pure neuritic leprosy, symmetric polyneuropathy, pansensory neuropathy, autonomic neuropathy, isolated cranial nerve involvement, leprous ganglionitis and radiculopathy.The demonstration of hypo-aesthetic skin lesions and mononeuropathies or mononeuritis multiplex strongly favours the diagnosis of leprosy. Slit skin smears (SSS) and electro-physiological evaluation is done in all patients as the next step, followed by skin biopsy when SSS is negative. US and MRN studies are reserved for difficult cases of pure neuritic leprosy when the diagnosis is unclear and to choose the site of nerve biopsy. Fascicular nerve biopsy is resorted to, in pure neuritis leprosy, when no other lead is forthcoming. Serological and molecular markers are used mainly in research settings and in diagnostic dilemmas.

5. Skin tests for the detection of Mycobacterial infections: achievements, current perspectives, and implications for other diseases

Duthie MS, Reed SG. Skin tests for the detection of Mycobacterial infections: achievements, current perspectives, and implications for other diseases. Appl Microbiol Biotechnol. 2021 Jan;105(2):503-508. doi: 10.1007/s00253-020-11062-4. Epub 2021 Jan 4. PMID: 33394146; PMCID: PMC7780083.

Immunological and molecular advances have modernized diagnostic testing for many diseases. Skin testing is a widely known diagnostic method used in allergy and infectious diseases involving intradermal injection of a small amount of antigen to assess either immediate IgE mediated allergic or antigen-specific T cell mediated delayed type hypersensitivity (DTH), responses.

Skin testing for leprosy has occurred with various antigen preparations generated by crude fractionation of M. leprae (Lepromin A, Rees Antigen, Dharmendra, and Convit's antigen) over the years. These have proven safe, and lepromin A has been used for nearly half a century. Analogous to the situation with TB, researcher used in vitro antigen recall data to prioritize the recombinant chimeric LID-1 fusion protein as a skin test candidate antigen for leprosy/M. leprae infection.

LID-1 was formulated to achieve maximum performance at a minimal dose in preclinical evaluation of DTH in M. leprae immune guinea pigs. Data indicated that intradermal inoculation of formulated LID-1 could satisfactorily distinguish uninfected from M. leprae–infected animals manifesting with symptoms distinctly similar to the PB presentation of patients, suggesting that evaluation among various groups in leprosy-endemic regions is merited.

6. Structure-Guided Computational Approaches to Unravel Druggable Proteomic Landscape of *Mycobacterium leprae*

Vedithi SC, Malhotra S, Acebrón-García-de-Eulate M, Matusevicius M, Torres PHM, Blundell TL. Structure-Guided Computational Approaches to Unravel Druggable Proteomic Landscape of Mycobacterium leprae. Front Mol Biosci. 2021 May 7;8:663301. doi: 10.3389/fmolb.2021.663301. PMID: 34026836; PMCID: PMC8138464.

Mycobacterium leprae is phylogenetically the closest bacterial species to *Mycobacterium tuberculosis (M. tuberculosis).* However, the *M. leprae* has a reduced genome of 3.2 Mbp, compared to 4.4 Mbp in *M. tuberculosis*, and survive with only 1,614 protein coding genes which are largely annotated based the features of their homologues in *M. tuberculosis* and other mycobacterial species. Determining the druggability of protein targets is important to avoid intractable targets. A druggable protein has the ability to bind with high affinity to a drug. In leprosy, the dihydropteroate synthase (DHPS), RNA polymerase (RNAP) and DNA gyrase (GYR) are known druggable proteins as they are the targets of Dapsone, Rifampicin and Ofloxacin, respectively. Nevertheless, protein druggability properties can be predicted by different bioinformatics tools based on the 3D structure/model of the protein. For example, the α-1,2-mannosyltransferase and mannosyltransferase proteins related to lipoarabinomannan pathway were identified as a possible drug targets using CASTp (Computer Altas of Surface Topography of proteins). In *Mycobacterium tuberculosis*, 2,809 proteins are identified as druggable using this *in-silico* approach.

Given the paucity of information related to structural proteomic studies in leprosy, authors discussed a multi-task protein modeling pipeline that enables proteome-scale template-based modeling of individual proteins encoded by various annotated genes in *M. leprae*. Homology-based structural and functional annotation of these protein models using appropriate computational tools for modeling and druggability assessment can expedite characterization of the structural proteome of *M. leprae* and accelerate structure-guided novel drug discovery to combat nerve damage associated with leprosy. Using the latest advancements in the field of protein structure bioinformatics, we describe our attempts to perform proteome scale modeling of mycobacterial genomes using in-house databases and pipelines. The modeled protein monomers or (homo/hetero) oligomers are subjected to multiple state-of-the-art validation scores. These models

can be very helpful and provide useful insights to understand protein structure and function, identify drug targets and unravel their functional roles in the pathogen.

7. Drug Delivery Systems on Leprosy Therapy: Moving Towards Eradication?

Chaves LL, Patriota Y, Soares-Sobrinho JL, Vieira ACC, Lima SAC, Reis S. Drug Delivery Systems on Leprosy Therapy: Moving Towards Eradication? Pharmaceutics. 2020 Dec 11;12(12):1202. doi: 10.3390/pharmaceutics12121202. PMID: 33322356; PMCID: PMC7763250.

The physicochemical characteristics of Dapsone and Clofazimine, in particular the poor-water solubility, hamper their therapeutic potential . The success of MDT depends on Dapsone and Clofazimine daily dosages, which often exhibit slow dissolution in the GIT, limiting oral bioavailability. Thus, often changes in the administered dosages are needed to reach the therapeutic range, and consequently may worsen toxic side effects. Strategies based on drug delivery systems address the drawbacks related to poorly water-soluble drugs by application of surfactant and lipids, co-solvents, nanocarriers, cyclodextrins and amorphous solid dispersions, among others.

Approaches to improve drugs solubility also include macromolecular systems, nanometric-sized drug delivery system such as liposomes, polymeric or lipid nanoparticles, pH-sensitive polymeric nanoparticles, transdermal drug delivery systems with incorporation of drugs in ethosomal gels.

8. A systematic review of Mycobacterium leprae DNA gyrase mutations and their impact on fluoroquinolone resistance

Chauffour A, Morel F, Reibel F, Petrella S, Mayer C, Cambau E, Aubry A. A systematic review of Mycobacterium leprae DNA gyrase mutations and their impact on fluoroquinolone resistance. Clin Microbiol Infect. 2021 Jul 12:S1198-743X(21)00381-5. doi: 10.1016/j.cmi.2021.07.007. Epub ahead of print. PMID: 34265461.

This study aimed at performing a systematic review (a) to characterize all DNA gyrase gene mutations described in clinical isolates of *M. leprae*, (b) to distinguish between those associated with FQ resistance or susceptibility and (c) to delineate a consensus numbering system for *M. leprae* GyrA and GyrB. In 25 included studies, 2884 *M. leprae* isolates were analyzed (2236 for gyrA only (77%) and 755 for both gyrA and gyrB (26%)):3.8% of isolates had gyrA mutations (n = 110), mostly at position 91 (n = 75, 68%) and 0.8% gyrB mutations (n = 6). Researchers concluded that mutations in DNA gyrase are observed in 4% of the *M. leprae* clinical isolates. To solve discrepancies among publications and to distinguish between mutations associated with FQ resistance or susceptibility, the consensus numbering system they proposed as well as the 3D model of the *M. leprae* gyrase for the evaluation of the impact of unknown mutations in FQ resistance, will provide help for resistance surveillance.

LEPROSY CLASS-1 IADVL

iadvl.mediknit.org

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NERVE FUNCTION ASSESSMENT IN LEPROSY

1. Sensory Examination
2. Nerve palpation
3. Motor examination

SENSORY EXAMINATION:

- On the skin lesion
- Along the nerve
- Face lesion
- Palms and sole
- Corneal sensation

Three types of sensation need to be checked

- Fine touch- wisp of cotton/SW filament
- Temperature- hot and cold water in test tubes
- Pain- Pin prick

Basic Principle of sensory examination

- Examine in day light
- Make the patient comfortable
- Maintain privacy
- Explain the patient before performing any procedure in her/his language
- Do a trial with eyes of the patient open
- Ask the patient to count each time he or she can locate the stimulus in open eyes
- Once the patients understands the procedure correctly ask him/her to close the eyes and repeat the procedure
- Always proceed from normal to abnormal (compare opposite side(normal area) and surrounding area)
- In regions with thicker skin (palms and soles) touch sensation can be tested with the tip of a ball-point pen gently, so as not to produce an indentation deeper than 2 mm
- Testing with Semmes-Weinstein monofilaments helps in detecting early hypoesthesia
- For child- fine touch difficult to elicit- temperature sensation
- For face lesions- complete anaesthesia not found, hypoesthesia should be elicited correctly
- For patients of PNL- hypoesthesia/anaesthesia along the nerve distribution is found

SW Mono-Filament

- 6 set Nylon monofilaments with calibration to produce specific force
- Green (0.05 gm), blue(0.2 gm), purple(2gm), red (4gm), orange(10 gm) and light red (300 gm)…detect normal, diminished light touch, diminished protective sensation, loss of protective sensation on hands, loss of protective sensation on feet and deep pressure sensation respectively
- Testing sites in Palms and soles**:** Hands- 3 sites each for median and ulnar and one site for radial nerve, Feet- 7 sites on sole for post tibial and 1 site dorsum of foot for deep peroneal nerve
- **Criteria for sensory impairment: A. Normal Reference threshold value:**Hand all sites- 0.2 gm, Foot- 2 gm and face- 0.05 gm B. **Sensory impairment:**

a. Monofilament threshold sensation increased by 3 or mor levels at one site or
b. Threshold increased by 2 levels at one site and one level in another site
c. Threshold increased by 1 level in all 3 sites for a nerve tested

Checking Corneal sensation:

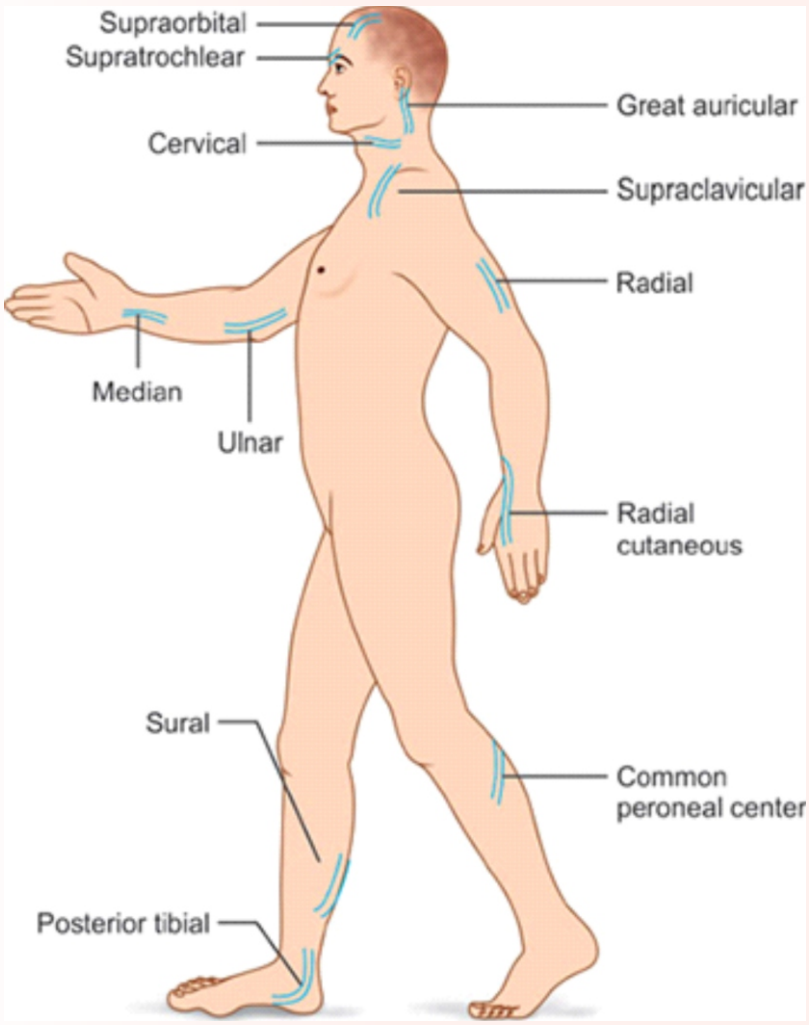
- Stand behind the patient
- From lateral side touch the tip of cotton at the limbus
- If patient blinks- intact corneal sensation

NERVE PALPATION

Basic Principles:

- Take the consent of patient and explain the procedure beforehand
- Always look at the face of patient while palpating
- Be gentle
- Use pulp of index, mid and ring fingers
- Compare both sides always
- Look for thickening, nodularity and tenderness
- If possible try to trace the nerve whole length – nodularity, abscess

Peripheral nerves examined in Leprosy:



Name of nerve	Site to be examined	Position of patient	Method of examination
Supra-orbital	Supraorbital notch at the junction of medial one-third and lateral two-thirds of supraorbital ridge	Sitting/standing with head kept straight	Palpate with both thumbs on both sides
Supra-trochlear	Medial to the supraorbital nerve	Sitting/standing with head kept straight	Palpate with both thumbs on both sides
Infra-orbital	Infraorbital foramen, just below the medial part of inferior orbital margin	Sitting/standing with head kept straight	Palpate with both thumbs on both sides
Facial	Zygomatic arch	Sitting/standing with head kept straight	Palpate with both thumbs on both sides
Great auricular	Lateral side of neck, crosses sternomastoid muscle, from lateral side to infra-auricular area	Sitting/standing with head turned completely to opposite side	Easily visible, crossing sternomastoid obliquely. May be palpated with 2 fingers
Transverse Cervical	Emerges along the posterior aspect of the sternocleidomastoid muscle inferior to the greater auricular nerve and passes anteriorly and horizontally along the sternocleidomastoid muscle	Sitting/standing with head turned completely to opposite side	Visible inferior to great auricular nerve
Supraclavicular(3 sets)	Shaft of clavicle	Sitting/standing straight	Roll fingers along the shafts of both clavicles
Radial	Spiral groove on humerus, posterior to the deltoid insertion	Sitting/standing with elbow flexed at 90° Examiner's right hand holds patient's right hand in shaking-hand manner and vice versa	With fingers palpate the nerve in the radial groove

Ulnar	Ulnar groove on medial epicondyle of humerus, medial to the point of elbow	Sitting/standing with elbow flexed at 90° Examiner's right hand holds patient's right hand in shaking-hand manner and vice versa	By little finger locate the nerve in the groove; other fingers palpate the nerve upward along medial aspect of arm
Radial Cutaneous	Lateral border of radius, just proximal to the wrist; thereafter along the proximal part of extensor pollicis longus tendon, which stands out prominently on ulnar side of the anatomical snuff box	Ask the patient to extend the thumb to visualize the anatomical snuff box	Roll the fingers against radius
Median	Proximal to the flexor aspect of wrist joint (proximal to flexor retinaculum), between the tendons of palmaris longus and flexor carpi radialis	Sitting/standing with elbow flexed at 90°, and wrist in supination. Examiner's left hand stabilizes patient's right hand and vice versa	With right fingers palpate the nerve deep between the tendons
Common Peroneal	Just below the lateral aspect of knee, along neck of fibula	Sitting with legs dangling freely	Thumb upper border of patella, Palpate up and down movement neck of fibula
Sural	Posterior aspect of leg, between the two bellies of gastrocnemius above and tendo-Achilles below	Standing/lying prone	Palpated on both sides by fingers and traced up to lateral border of foot
Anterior Tibial	On the dorsum of foot, lateral to the tendon of extensor hallucis longus and dorsalis pedis artery	Patient sitting on bed with legs straight and is asked to extend the great toe to make the extensor hallucis longus tendon stand out	Palpated by rolling of fingers
Posterior Tibial	Medial aspect of ankle (deep to flexor retinaculum) between medial malleolus and tendo Achilles	Sitting on bed with knee flexed/standing	Palpated by rolling of fingers

MANAGEMENT OF NEURITIS

Major goals:

1. Early detection of nerve involvement
2. Appropriate treatment
3. Adequate care for the prevention of disabilities and rehabilitation

Management:

a. Supportive

b. Medical

c. Surgical

- ***Supportive management***:
- Rest
    - Splinting in semi relaxed position
    - Heat therapy
        - Ultrasonic therapy
        - Short wave diathermy
    - Physiotherapy during recovery

    - Counseling
    - Recovery of NFI varies
        - Duration of NFI
        - Extent of damage
        - Severity of reaction
        - General health
        - Type of leprosy
        - Adequacy of treatment
    - New NFI may occur while on MDT
- ***Medical therapy:***
    - Continue MDT
    - Anti-inflammatory drugs
        - Analgesics
        - Corticosteroids
        - Clofazimine
        - Thalidomide
        - Others
            - Azathioprine
            - Cyclosporine

Analgesics(Aspirin ,Ibuprofen and Paracetamol): Reduce pain and swelling

Corticosteroids:

- Mainstay of therapy
- Rapid improvement
    - Anti inflammatory
    - Immunosuppressive
    - Anti-fibrotic – reduce post inflammatory scar – important for improvement in nerve function

Treatment regime for field workers (WHO):

Weeks	Dose of prednisolone(mg)
1-2	40
3-4	30
5-6	20
7-8	15
9-10	10
11-12	5

Treatment regime ILEP

Weeks	Dose of prednisolone(mg)	Weeks	Dose of prednisolone (mg)
1-2	40	1-4	40
3-4	30	5-8	30
5-6	20	9-12	20
7-8	15	13-16	15
9-10	10	17-20	10
11-12	5	21-24	5

Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1):

- Prednisolone 20mg/d x 3 months; tapering doses in 4th month + MDT **V/S** MDT + placebo
- Use of low dose prophylactic prednisolone during the first four months of multidrug treatment for leprosy reduces the incidence of new reactions and nerve function impairment in the short term, but the effect is not sustained at one year

The prognostic importance of detecting mild sensory impairment in leprosy: A randomised controlled trial (TRIPOD 2):

- Sensory impairment detected by ball point pen vs nylon filaments
- Prednisolone treatment starting at 40 mg per day, tapering over 4 months, or placebo
- No improvement in long term outcomes in terms of recovery of touch sensibility
- Strong tendency of spontaneous improvement of mild sensory impairment

Treatment with corticosteroids of long standing nerve function impairment in leprosy: A randomised controlled trial (TRIPOD 3):

- Patients with untreated NFI between 6 and 24 months
- Randomised
    - Prednisolone treatment starting at 40 mg/day, tapered by 5 mg every 2 weeks, and completed after 16 weeks
    - Placebo
- No demonstrable additional improvement in nerve function, or in preventing further leprosy reaction events was seen in the prednisolone group

- The trial confirms current practice not to treat long-standing NFI with prednisolone
-
- Clofazimine:
    - Anti leprosy action
    - Anti inflammatory action
        - Reduces granulocyte chemotaxis
        - Alters function of phagocytes
        - Increases number of lysosomes
        - Inhibits lymphocyte transformation
- Dosing: 300 mg for 12 weeks followed by 200 mg for 12 weeks followed by 100 mg for 12 to 24 weeks. Total duration of treatment should not be more than one year.
- Adverse effects**:** Reddish brown discoloration of skin, icthyosis(anticholinergic action), transient rash and enteropathy
- Thalidomide:
    - Reduces chemotactic factors
    - Reduction in CD4 lymphocytes
    - Decreases IL 12 production
    - Reduces TNF α, IFN gamma

- Dosing: 400 mg/day, 300 mg/day within a week, reduced 100 mg/month and Stabilize on lowest dose for 2-3 months
- Adverse effects
    - Teratogenecity
    - Sedation
    - Constipation
    - Peripheral neuropathy
    - Thromboembolism
    - Hypothyroidism
- Intra/perineural injections:
    - Corticosteroid
    - Vasodilators – Isoxsuprine, tolazoline
    - Platelet rich plasma
    - Caution –
        - Severe pain during injection
        - Potential of nerve damage
- **Surgical therapy:**

- Neurolysis:
    - Restore sensation in 50% cases
    - Improves muscular function
    - Pain relief
    - Fastens ulcer healing
    - **Indications**

Associated Tuberculosis:

- Steroids prescribed under proper ATT cover

- Latest National guidelines to be followed

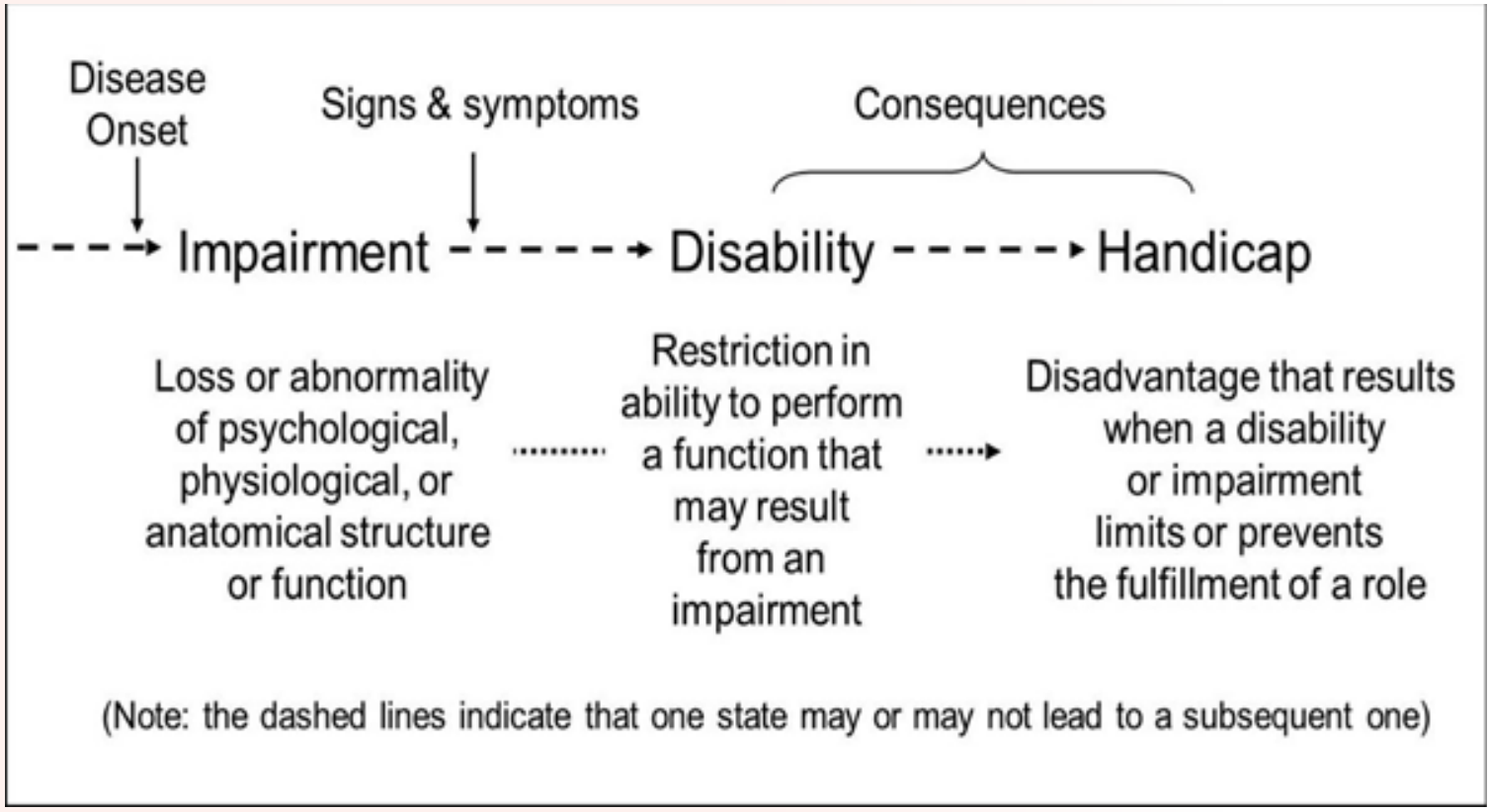
Neuritis after completion of MDT:

- Steroids should be given along with an anti leprosy medicine
- Clofazimine may be given alone due to anti inflammatory as well as anti leprosy action

New NFI developing while on MDT:

- High risk subset
    - Higher average BI
    - BL, LL
    - Late detection
- Persistent immune response to dead bacilli
- Strict regime is not followed and treatment is individualized for each patient
- > 20 weeks course may be needed
- Dapsone induced neuropathy to be kept in mind

DISABILITY ASSESSMENT



- No improvement on steroids
- Steroids are contraindicated or not tolerated
- Intractable pain
- Sudden paralysis

Works complimentary with steroids

- Extra neural
  - Constricting fibrous bands excised
  - Relieves external pressure
- Intraneural : Longitudinal incisions given in nerve sheath
- Interfascicular :Individual nerve bundles dissected

Nerve abscess drainage

- Always drain
- Longitudinal incision
- Remove necrotic material
- Remove surrounding adherent slough
- Meticulous procedure

Nerve transposition

- To avoid nerve stretching
- To increase blood supply to nerve
- To prevent nerve injury by burying the nerve in muscle

Usually done for ulnar nerve at elbow

Complications

- Unavoidable nerve injury
- Painful scars
- Hematoma
- Secondary infection
- Damage to vessels and tendons

Special Situations

Neuritis in Pregnancy:

- Steroids to be used minimally
- Fetal growth retardation
- Fetal adrenal suppression
- Instead of 40 mg- 30 mg starting dose, taper in 10 (12)weeks (PB) and taper in 20 (24) weeks (MB)

Neuritis in children:

- Steroids should be used judiciously
- Dose **1mg/kg/d**
- Alternate day dosing better
- PB- 1mg/kg/d x 2 weeksà 1mg/kg on A/D x 2 weeksà gradual taper over 10 weeks
- MB- similar dosing; duration of each stage doubled

In leprosy loss of finger: Impairment
Inability to write/hold things: Disability
Loss of earlier occupation: Handicap

Primary and secondary impairments in Leprosy due to nerve damage:

The primary impairments occur because of nerve damage in leprosy whereas the impairments resulting out of primary impairments are called secondary.

Primary Impairments	Secondary Impairments
Face Lagophthalmos Corneal anesthesia	Stiff Joints Joint Contractures Shortening Ulcers Disintegration of bones Exposure keratitis, corneal ulcer, and corneal opacity
Hand Ulnar clawing ape thumb deformity total lawing Wrist drop/Finger drop	
Feet Foot drop Claw toes Plantar anesthesia	

WHO grading of impairments: The WHO grading system has separate components for hands, feet, and eyes.

WHO disability grades for Hands and Feet	
0	Absence of anesthesia and absence of any visible impairments in the hands and feet
1	Presence of anesthesia and absence of visible impairments in the hands and feet
2	Presence of visible impairment in the hands and/or feet

WHO disability grades for EYE	
0	No eye problems due to leprosy and no visual loss
1	Eye problems due to leprosy but vision not affected (Vision is 6/60 or better; can count finger at 6 meters)
2	Severe impairment to vision (Vision is worse than 6/60; cannot count fingers at 6 meters)

Motor Assessment:

Orbicularis oculi: The muscle is supplied by Zygomatic and temporal branches of facial nerve. Ask the patient to close the eyes forcefully and try to separate the eyelids. With normal muscle power separation of eyelids is quite difficult and easy opening/separation indicated weakness of muscle which results in lagophthalmos.

Extensors of wrist joint: The muscles are supplied by posterior interosseous branch of radial nerve. The patient is asked to close fist and dorsiflex the wrist against resistance. Inability to extend the wrist and fingers suggests radial nerve involvement and results in wrist drop.

Flexor digitorum superficialis and profundus (lateral part) (Ochsner's clasping test):
Patient asked to clasp both hands, in case of median nerve weakness the index finger of affected side will remain straight with flexion of other fingers (Pointing index/Benediction sign).

Abductor pollicis brevis (Pen test): The muscle is supplied by median nerve. Patients hand is laid flat (palmar surface up) on a table and asked to touch a pen held slightly higher, by moving the thumb vertically up (abduction). Inability to touch the pen suggests loss of abduction due to median nerve weakness which results in ape thumb deformity.

Opponens pollicis: Stabilize the patients hand with own and asked the patient to swing thumb across the palm (the thumb-nail lying parallel to palm) to touch the tips of other fingers and try to resist the patient's action with own index finger. Inability to perform the action against the resistance indicated weakess of opponens pollicis.

First palmar interossei and adductor pollicis (Book test): The muscles are supplied by the deep branch of ulnar nerve. Patient asked to hold a book between two hands by keeping the adducted thumbs straight on its upper surface. Try to pull the book in opposite direction. Flexion of the distal IP joint of thumb (Froment's sign) with hyperextension of MCP joint on affected side indicates weakness of these two muscles and action of flexor pollicis longus (median nerve). There occurs guttering of 1st interosseous space.

Lumbricals + interossei: 1st and 2nd lumbricals are supplied by median nerve whereas 3rd and 4th lumbricals are supplied by deep branch of ulnar nerve. The Interossei are supplied by deep branch of ulnar nerve.The patient is asked to flex the fingers at MCP joints against resistance. Inability to do so indicates weakness of these muscles and results in claw hand(hyperextension at MCP and flexion at IP joints). Partial claw hand (1st, 2nd, 3rd or 4th and 5th fingers): only median nerve or only ulnar nerve involvement; Complete claw hand (all fingers): both median and ulnar nerve involvement.

Palmar interossei (Card test): The muscles are supplied by deep branch of ulnar nerve. Patient asked to keep fingers extended as well as adducted. A firm paper-card is inserted in each web-space serially and patient is instructed to grasp it tightly while the examiner tries to pull it out. Inability to hold the card tightly indicated weakness of the muscles. Subtle abduction of little finger (Wartberg's sign) is the earliest sign of ulnar nerve involvement. There occurs guttering of interosseous spaces.

Dorsal interossei: These muscles are supplied by deep branch of ulnar nerve. Patient asked to spread out fingers against resistance by examiner's hand. Inability to do so indicates muscle weakness and later on results in guttering of interosseous spaces.

Dorsiflexors of ankle(Extensor hallucis longus Peronei longus and brevis): These muscles are supplied by common peroneal Nerve. Patient asked to perform dorsiflexion at ankle, extension of great toe and eversion of foot against resistance and inability to the movement indicates weakness which results in foot drop.

Intrinsic muscles of feet: The muscles are supplied by medial and lateral plantar branches of tibial nerve. Patient asked to adduct/abduct toes against resistance. Inability to do so indicates weakness of the muscles. Weakness results in collapse of arch of foot, guttering of inter-tarsal spaces and claw toes.

LEPROSY CLASS-2 IADVL

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TROPHIC ULCER :

- An ulcer due to impaired nutrition to the part
- An anaesthetic deformity (In Leprosy)
- A common sequel of Grade II disability
- Characteristics :
    1. Callus formed around the ulcer
    2. Accompanied by anaesthesia
- Dynamic and/or static deformity + numbness + constant high pressure leads to trophic ulcer
- Neurogenic ulcers (causes)
    - Leprosy
    - Diabetic Neuropathy
    - Alcoholic
    - Paraplegia
    - Spina Bifida
    - Syringomyelia

TROPHIC ULCER IN LEPROSY :

- Most common – Sole
    - 70-90 % - Forepart of the sole
    - 5 – 10% - Heel & mid lateral border
    - 1 – 5% - Toe tips

- Extraplantar
    - Dorsal aspect of foot
    - Ankle-lateral malleolus
    - Tips of elbows
    - Proximal palmar surface
    - Volar aspect of hands

PATHOGENESIS :

- Walking on insensitive foot
- Intrinsic muscle paralysis
- Infections/ deep fissures

} COMMON

- Autonomic Nerve Damage
- Previous Scar Tissue
- Vascular Insufficiency
- Direct action of M.Leprae

} RARE

GAIT CYCLE :

- Stance
- Loading response
- Mid-stance – Heel rise
- Pre-swing / Initial swing
- Toe off

STAGES OF ULCER :

- Threatened ulcer
  - Deep edema
  - Puffiness
  - Gap between toes
  - Tender
- Concealed ulcer
- Overt ulcer

TYPES OF ULCER

- Acute Ulcer
  - Infection
  - Inflammation

- Erythematous edges
- Slough

- Chronic Ulcer
  - Scant discharge
  - Heaped-up edges
  - Pale granulation tissue
- Complicated Ulcer
  - Osteomyelitis
  - Malignancy
- Recurrent Ulcer
  - Infection
  - Lack of care
  - Continuous pressure

MANAGEMENT :

ASSESSMENT OF NEUROPATHY :

- Ten gram Semmes-Weinstein monofilaments
- Self measurement of sole temperature
- Dynamic plantar pressure measurement

X-RAY

- Forefoot/ mid-foot – Dorsoplantar view
- Heel – Lateral View
- Tarsal inf – Dorsoplantar/ Lateral/ Oblique view

MANAGEMENT ALGORITHM :

- Dressings
- Antibiotics
- Debridement
- Growth factors
- Surgical modality for bone involvement
- Boots to reduce pressure
- Lifestyle changes

THREATENED ULCER :

- Absolute rest
- No weight bearing
- Leg elevation for 2-3 days
- Foot care

CONCEALED ULCER :

- Do not break the blister
- If needed – strip the blister and cover with sterile Vaseline gauze
- Below knee plaster cast – walk after 3 days
- Plaster cast for 3 weeks
- Foot care/ protective footwear

OVERT ULCER :

- ACUTE ULCER – Antibiotics/ Rest/ Debridement/ Dressing
- UNCOMPLICATED CHRONIC ULCER – Below knee cast x 6 weeks / Zinc oxide Adhesive plaster
- COMPLICATED CHRONIC ULCER- Debridement

MOIST WOUND DRESSINGS : Help in rapid migration of keratinocytes around wound bed

AMWT – Advanced Moist Wound Therapy – Hydrogels and Alginates

DRESSING MATERIAL SELECTION :

- Silver Cation – Eliminates antibiotic resistant bacteria
- Silver barrier dressing destroys bacteria within the wound
- Exudation wound – Hydrocolloid dressing

PRESSURE OFF-LOAD :

- Total contact casting
- Wheel chair/ Waterbeds

WOUND MANAGEMENT :

- Hyperbaric Oxygen Therapy
- Debridement
- PRFM Dressing

OTHERS :

- Becaplermin gel

- Low level Laser Light
- Topical Insulin
- Topical Phenytoin Sodium
- Artificial Skin

SURGERY: Split thickness grafts/ flaps

PREVENTION OF RECURRENCE:

- Metatarsal bars/ Arch support/ Weight relieving calipers
- Walk – 30 min – Rest
- Keep skin hydrated / Urea cream
- MCR footwear – Soft insole/ Hard outsole/ Straps – Front & back

SURGICAL MANAGEMENT - LEPROSY DEFORMITIES:

- To prevent further deterioration
- To improve physical/ cosmetic condition
- To improve patients' quality of life and ability to use hands/ feet/ eyes safely
- To improve social participation

CRITERIA FOR SELECTING A CASE FOR SURGERY :

1. Muscle paralysis should be present for at least one year
2. Age 15-45 yrs
3. There should be no infections/ wounds/ ulcers
4. Patient should have completed at least 6 months of MDT
5. Free from reaction & symptomatic neuritis for at least 6 years
6. Low BI preferably
7. Not on steroids for the past 6 months unless the surgery is for neuritis

CONDITIONS REQUIRING SURGICAL INTERVENTION:

- Irreversible claw hand/ foot drop/ claw toes
- Lagophthalmos/ Nasal deformities
- Triple nerve paralysis
- Nerve abscess where nerve decompression is needed

FOOT DROP:

High stepping gait – Ball of foot hits the ground instead of the heel – there is inability to dorsiflex and evert the foot actively

Tibialis posterior tendon transfer operation

Provides strength for dorsiflexion of ankle and maintaining mid-position of foot (neither inversion nor eversion)

2 ways

Interosseous route ← → Circumtibial route

Tendon to tendon fixation offers better results than bone fixation and periosteal fixation.

CLAW TOE **:**

- Flexor to extensor claw toe correction
- Helps to release contraction
- Transfer of Flexor digitorum longus to each toe to the dorsal expansion – so that FDL functions like the paralyzed intrinsic muscle and clawing of toe is abolished.

CLAW HAND **:**

- Claw finger + Loss of thumb apposition

3 TYPES OF FUNCTIONAL PINCH (THUMB APPOSITION) :

1. Key pinch – Pulp of the thump apposed to sides of index finger
2. Two finger pinch
3. Three finger pinch – Holding a pen while writing

INTRINSIC ZERO THUMB **:**

- When all the muscles are paralyzed, the thumb cannot abduct or oppose. It can only extend. This severely restricts the usefulness of the thumb. Occurs mainly because of combined Ulnar and Median nerve paralysis.

STANDARD OPPONENS PLASTICS :COMMON

- Flexor digitorum superficialis transfer
- Extensor indicis transfer
- Palmaris longus transfer
- Extensor pollicis transfer
- Flexor carpi ulnaris transfer

} COMMON

THE RESTORATION OF THUMB FUNCTION **:**

- Pinch and grasp – By Opponens replacement – provides stability & strength of rthumb interphalangeal extension of CMP-MCP abduction, opponens and flexion.

LAGOPHTHALMOS : Temporalis transfer flap

PHYSIOTHERAPY IN LEPROSY :

REHABILITATION :

- Restoration to the fullest physical, mental, social, vocational & economic usefulness of which the patient is capable.

ROLE OF EXERCISE THERAPY :

- To strengthen weak muscles
- To prevent contraction & to reduce the existing contracture
- Restoration of functions
- To educate patients about self care
- Pre/ post-op exercise with reconstructive surgeries

RANGE OF MOTION (ROM) :

- Active ROM & Passive ROM
- Active ROM never exceeds passive ROM
- If both are normal, then there is no abnormality
- If Active ROM is less than Passive ROM, it indicates :
    A. Muscle power is non-functional
    B. Discomfort exists during joint movement
    C. Combination of A & B
- If Active ROM is the same as Passive ROM, but less than normal ROM, this indicates that the muscle power is functional within the limited range, a contracture exists or some pathology is present in the joint.

EXERCISE TO IMPROVE ROM :

- Each joint should be stretched separately, particularly true in the contraction of the finger joint
- In order to stretch a joint, grasp the area to be stretched above and below the joint to stabilize it.
- The extremity should be pulled slightly and stretched
- Frequency – exercise twice a day for about an hour

OBJECTIVE OF PRE-OP EXERCISES :

- To increase the ROM of the joint which is involved
- To increase the muscle power which will be necessary for most of the parts of the body after surgery

EXERCISE POSE RECONSTRUCTIVE SURGERY :

- Exercise begins post cast removal

EHF SCORE :

- Calculate the sum of WHO Scores for each Eye/ Hand & foot

FACIAL NERVE EXERCISES :

- ACTIVE ASSISTED EXERCISE – Patient should try to tightly close the eye – hold for 10-20 counts – then open the eye.
- PASSIVE ASSISTED EXERCISE – Patient should place the index finger at the lateral side of the eye and pull the eyelid laterally so that eye closes.

ULNAR NERVE EXERCISES :

- ACTIVE – Place the palm on the table – Adduct & abduct fingers – Keep MCP in flexion/ wrist in neutral
- PASSIVE – Gently straighten the finger of the claw hand using the other unaffected hand.
- ACTIVE ASSISTED EXERCISE – MCP of affected hand – supported at 90° by the other hand.

MULTIPLE CHOICE QUESTIONS

Dr Swastika Suvirya
Additional Professor and Head, King George's Medical university
Dr Usha Chandra
Senior Resident

1. In lepromatous leprosy with type 2 reaction elevated levels of which of the following in serum might increase chances for acquiring severe COVID-19 infection?

   A. Prolactin

   B. C reactive protein

   C. Lactose Dehydrogenase

   D. Alkaline phosphatase

2. When compared to the genome of Mycobacterium tuberculosis, M. leprae underwent which type of evolution?

   A. Reductive evolution

   B. Divergent evolution

   C. Convergent evolution

   D. Parallel evolution

3. Possible biomarkers of subclinical infection of household contact, and also a parameter of early infection monitoring.

   A. CCL2 chemokine, IFN-γ

   B. CCL4 chemokine, IFN-α

   C. CCL2 chemokine, IFN-α

   D. Chemokines CXCL8, CXCL9 and CXCL10

4. Incorrect statement regarding the risk factors for physical disability in patients with leprosy?

   A. Female patients were almost 2 times more likely than male patients to have physical disability.

   B. Men often ignore leprosy symptoms and seek health services at more advanced stages of the disease and

with more severe clinical manifestations male sex, multibacillary leprosy, leprosy reactions, and lepromatous presentation

C. Although tuberculoid and indeterminate leprosy are the most frequent clinical presentations but patients with lepromatous leprosy have 5- to 12-fold greater odds of disability

D. Patients with lepromatous forms were more likely to have disability than patients with borderline forms, tuberculoid, or indeterminate leprosy

5. Which of the statement about enhanced chemoprophylaxis in Leprosy PEP++ is incorrect?

A. It will reduce the risk to develop the disease and will stop the transmission of leprosy by preventing new cases

B. Three standard doses of rifampicin 600 mg plus moxifloxacin 400 mg given at four-weekly intervals

C. Three standard doses of rifampicin 600 mg plus clarithromycin 300 mg (weight adjusted) given at four-weekly intervals in those with contraindications to moxifloxacin

D. BCG re-vaccination in combination with the single-dose rifampicin

6. Socioeconomic risk markers of leprosy are?

A. Increased age, poor sanitary and socioeconomic conditions, lower level of education, living in a crowded household (≥5 per household) ,lack of clean water

B. Increased age, poor sanitary and socioeconomic conditions, lower level of education, food-insecurity, being female

C. Increased age, poor sanitary and socioeconomic conditions, lower level of education, and food-insecurity, suffering from food shortage in the past, being male

D. Preschooler age, poor sanitary and socioeconomic conditions, lower level of education, and food-insecurity suffering from food shortage in the past, lack of clean water

7. As per recent advancement in diagnosis of Hansen disease, which is the incorrect statement–

A. Leprosy can be distinguished from sarcoidosis by quantitative study of reticulin fibers present in skin.

B. Leprosy can be distinguished from sarcoidosis by qualitative study of reticulin fibers present in skin

C. The studies of micro RNAs (miRNAs) made it easy to differentiate leprosy from other diseases especially from tuberculosis.

D. The role of vitamin D and vitamin D receptors (VDR) made the diagnosis of leprosy easier at early stages

8. For chemoprophylaxis in leprosy, all of the following drug regimes are effective except:

A. Rifampicin/RFM (single dose of 300 to 600 mg)

B. Dapsone/DDS (50 or 100 mg once or twice a week for 2 years)

C. Acedapsone (an intramuscular injection of 225 mg every 10 weeks for 7 months)

D. BCG vaccine combined with RFM

9. What is the percentage of sensitivity and loss of touch sensation in a lesion of Hansen disease –

A. 48%

B. 90%

C. 20%

D. Variable

10. Slit Skin Smear can be used in diagnosis of –

A. Hansen disease, cutaneous mastocytosis, cutaneous leishmaniasis

B. Hansen disease

C. Cutaneous mastocytosis, Cutaneous leishmaniasis

D. Cutaneous leishmaniasis only

Ans 1 – C. (Rathod S, Suneetha S, Narang Tetal. Management of leprosy in the context of COVID-19 pandemic: Recommendations by SIG leprosy (IADVL academy). Indian Dermatol Online J 2020;11: 345-8)

Ans 2 - A (Lastória JC, Abreu MA. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - part 1. An Bras Dermatol. 2014;89(2):205-218.)

Ans 3 – A. (Queiroz EA, Medeiros NI, Mattos RT, et al. CCL2 and IFN-γ serum levels as biomarkers for subclinical infection in household contacts of leprosy patients. MicrobPathog. 2021;150:104725. doi:10.1016/j.micpath.2020.104725)

Ans 4 - A (De Paula HL, De Souza CDF, Silva SR, et al. Risk Factors for Physical Disability in Patients with Leprosy: A Systematic Review and Meta-analysis [published online ahead of print, 2019 Aug 7]. JAMA Dermatol. 2019;155(10):1120-1128. doi:10.1001/jamadermatol.2019.1768)

Ans 5 – D (Palit A, Kar HK. Prevention of transmission of leprosy: The current scenario. Indian J Dermatol Venereol Leprol. 2020 Mar-Apr;86(2):115-123.)

Ans 6 – C (Pescarini JM, Strina A, Nery JS etal. Socioeconomic risk markers of leprosy in high-burden countries: A systematic review and meta-analysis. PLoSNegl Trop Dis. 2018 Jul 9;12(7):e0006622.)

Ans 7 – B (Aamir M, Sadaf A, Khan S, Perveen S, Khan A. Recent Advancement in the Diagnosis and Treatment of Leprosy. Curr Top Med Chem. 2018;18(18):1550-1558.)

Ans 8 – D (Reveiz L, Buendía JA, Téllez D. Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis. Rev PanamSalud Publica. 2009;26:341:9–341:9.)

Ans 9 - D (Kumar B, Dogra S. Leprosy: A disease with diagnostic and management challenges ! . Indian J Dermatol VenereolLeprol2009;75: 111-115)

Ans 10 - A (Gautam M, Jaiswal A. Forgetting the cardinal sign is a cardinal sin: Slit-skin smear. Indian J Paediatr Dermatol 2019;20:341-4)

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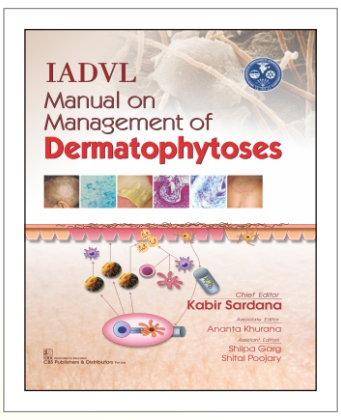

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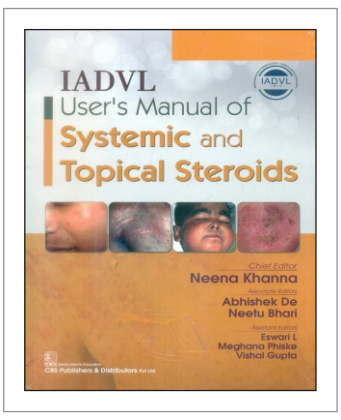

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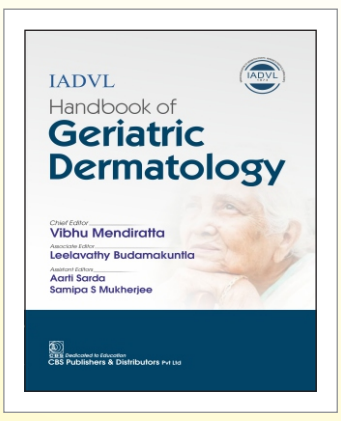

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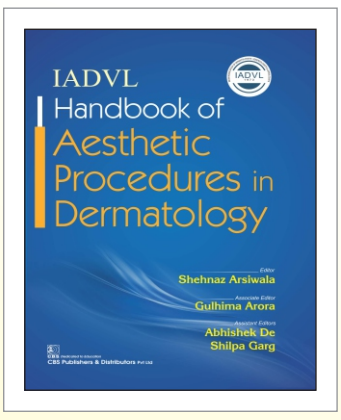

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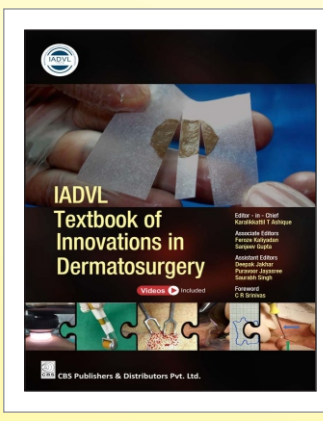

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