HRSA

NHDP Guide to the Management of Hansen's Disease

National Hansen's Disease Program

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INTRODUCTION

Treatment has dramatically changed over the past century for people diagnosed with Hansen's disease (HD or leprosy) in the United States. Prior to 1950, confinement at the National Leprosarium in Carville, Louisiana was the only option. The discovery of an effective drug regimen and the establishment of Ambulatory Care Programs (ACP) in select cities now allow patients to be treated in proximity to their homes. Only patients who experience severe complications that cannot be managed by local providers are brought to the National Hansen's Disease Program's (NHDP) Baton Rouge headquarters for treatment. There are many private physicians who also treat HD. Since the number of physicians who provide treatment has increased, a standardized guide for the care of HD in the U.S. is essential.

Objective

The purpose of this manual is to serve as a practical guide for healthcare professionals directly involved in the diagnosis and treatment of people with HD in the United States and its territories. It may also be a valuable tool as an overview of HD for medical students, residents, and others interested in the disease.

Mission

The NHDP is a medical service within the Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), Health Systems Bureau (HSB). NHDP is authorized by Public Law99-177, Section 2, (a), Section 320 and is guided by DHHS regulations. The NHDP mission is to provide diagnosis, treatment, and education for Hansen's disease in the U.S. and its territories. Through its clinical, research, and training programs, NHDP addresses Hansen's disease, its associated disabilities, and stigma. NHDP uniquely focuses on the full spectrum of the disease by researching causation, transmission, and prevention.

Eligibility

Individuals living in the United States, or its territories, may receive outpatient medical carefor the diagnosis and treatment of HD and its complications. Ideally, individuals are diagnosed and treated locally; however, eligibility for patient care at the NHDP in Baton Rouge, LA is assessed by the NHDP Clinical Care Conference Team on a case-by-case basis. Decisions are contingent upon answers to the following questions:

1. Is the patient's problem related to HD?
2. Can this problem be solved locally for the patient?
3. Can NHDP successfully treat this problem if the patient cannot receive treatment locally?
4. Does the patient have any additional health complications that would interfere with treatment or require more intensive care than can be provided at the NHDP?

Contacts of known patients are also eligible for HD related services as described by NHDP policy (see "Contact Evaluation" in Section XIV).

HISTORY OF HANSEN'S DISEASE

The earliest written description of leprosy (HD) was recorded in India during the sixth millennium BC. The cause, however, remained unknown until 1873 when Dr. Gerhard Armauer Hansen (for whom the disease was renamed) of Norway identified *Mycobacterium leprae* as the bacteria responsible for the disease. Various palliative therapies were tried, but none proved effective, and most people were relegated to a life of isolation and abandonment. In 1941, sulfone drugs were first used to treat HD at the National Leprosarium in Carville, Louisiana, andby 1950, dapsone had become the standard treatment. The rapid improvement in patients treated with dapsone therapy led to hopes of the eradication of HD, and the search began in earnest for even more powerful drugs. However, there were no effective animal models at the time and *M. leprae* still cannot be cultivated in artificial media. In 1960, Charles Shepard described the limited multiplication of *M. leprae* in the mouse footpad, which made it possible for the first time to screen drugs for anti-leprosy activity and detect drug resistance. Since then, armadillos,nude mice, and a variety of immunosuppressed mice have been used to obtain higher yieldsof *M. leprae* for bacteriological and immunological studies. The World Health Organization (WHO) introduced multidrug therapy (MDT) to the global community in 1982.

Today, HD drugs are distributed free of charge around most of the world through WHO by the Novartis Foundation. NHDP provides medications at no cost to diagnosed patients living in the US and its territories. Because of these efforts, the global burden of disease has fallen dramatically in recent decades.

OVERVIEW OF *M. LEPRAE*

Bacteriology

Mycobacterium leprae is a weakly acid-fast rod, 2-8 microns long and 0.3 microns in diameter. It is an obligate intracellular organism and can be found in tissues singly or in clumps (globi) whichmay contain hundreds of bacilli. *M. leprae* will survive for a short period in tissue cultures. Limited metabolism (but not multiplication) can take place in some types of special laboratory media. Consistent multiplication occurs following injection of viable bacilli into the footpads of mice, as well as in nine-banded armadillos.

The generally accepted generation time of *M. leprae* is approximately 12 days. This very slow rate of multiplication is consistent with the long (usually 3-5 years) incubation periodof HD in humans required to manifest symptoms.

M. leprae DNA can be identified in tissue biopsies by using the nucleic acid amplification technique, polymerase chain reaction (PCR). Genotyping of *M. leprae* DNA has demonstrated several major genotypes and revealed that armadillos and humans in the United States share some genotypes. *M. leprae* from biopsies can also be tested for mutations associated with drug resistance.

Since its discovery by Gerhard Armauer Hansen, *M. leprae* was thought to be the only bacterium to cause leprosy. In December 2008, the American Journal of Clinical Pathology

published an original article by X. Han, MD, PhD., *et. al.* documenting the discovery of a “new Mycobacterium strain” (Am J Clin Pathol 2008; 130:856-864). The comparison showed this “new strain” to be a new species of Mycobacterium. This new species has been named *Mycobacterium lepromatosis*. Cases of *M. lepromatosis* have been reported in Canada, Asia, several provinces of Mexico, and South and Central America(Jessamine 2012, Sotiriou 2016, Han 2014).

M. lepromatosis, is genetically distinct from *M. leprae*, but shares striking evolutionary and biologic similarities*. M. lepromatosis* manifests with the same broad spectrum of cutaneous and neurologic findings that are described in HD and is comparable to infection with *M. leprae*. Reactions-Type 1 reversal and Type 2 ENL can occur with both *M. leprae* and *M. lepromatosis*. There is insufficient evidence to determine if immunologic reactions with *M. lepromatosis* are more severe. *M. lepromatosis* could be the causative agent of several cases of DLL (Diffuse Lepromatous Leprosy) with presentations like that seen in patients who develop Lucio’s phenomenon (Han 2008). To date, no clear clinical or histopathologic differences between infections with the two species can be recognized andthus, differentiating them is mostly of epidemiologic value. Importantly, multi-drug therapy appears to be effective for both infections and therefore, one diagnosis does not seem to portend a more ominous disease course than the other.

Immunology

The Host Response

Only 3 to 5 percent of the world’s population appears to be susceptible to clinically detectable infection with *M. leprae*. Among susceptible individuals, a wide range of clinical manifestations is seen based on the individual’s cell-mediated immune (CMI) responses to *M. leprae.* The histopathological spectrum found in lesion biopsies correlates with the different clinical forms and is used for the classification of HD. At the tuberculoid end of the spectrum, there is a good host CMI response that localizes the disease. At the lepromatous end of the spectrum, CMI response to *M. leprae* is weak or absent and the disease may affect skin, nerves, eyes, lymph nodes, muscle, and internal viscera such as the liver. In the middle of the spectrum, known as borderline HD, various clinical presentations between the two extremes are seen, reflecting the variation in host responses. (Classification of HD is described in Section IV.)

Immunodeficiency due to HIV infection or medical immunosuppression, such as transplantation or cancer chemotherapy, will render individuals more susceptible.

Similar increases in susceptibility may occur in individuals taking corticosteroids ornewer biologic treatments for arthritis or autoimmune diseases.

The Lepromin Test

The Lepromin skin test is not a diagnostic test, and the reagent is no longer available. Historical information about this test can be found in medical literature.

Skin and Nerve Involvement

M. leprae and *M. lepromatosis* have a particular affinity for skin and peripheral nerves. In the skin, they are found in macrophages where, in lepromatous HD, the bacteria are able to survive and multiply to form large masses of bacilli ("globi"). In nerves, they are found within

macrophages and Schwann cells. The presence of acid-fast bacilli in nerves is pathognomonic of HD.

Epidemiology

HD is found primarily in tropical and sub-tropical regions. Approximately 25 percent of the world's population live in areas where they might be exposed to the infection. Because of stigma and other reporting issues, it remains difficult to get an accurate estimate of the global number of HD cases.

The NHDP is the federal agency primarily responsible for the care, treatment, and control of Hansen's disease in the United States. The disease has been reported among individuals from every state. Since the 1990's, an average of 180 new cases are reported annually. In the last decade, patient demographic data from NHDP demonstrates ~40% of the cases are U.S. born, ~40% are foreign born, while ~20% are from US territories and Compacts of Free Association (COFA) nations.

Transmission:

The exact mode of transmission of *M. leprae* is poorly understood. The evidence suggests that optimal transmission appears to occur in a setting of prolonged, close contact, and not from casual contact. It is thought to be transmitted between people primarily via the respiratory route. However, the disease is not highly contagious. Approximately 95-97% of the world's population appear to be naturally immune to HD.

Nine-banded armadillos are also significant reservoirs for *M. leprae*. Studies show that in the United States transmission occurs between armadillos and humans, but the mode is unknown.

CLASSIFICATION AND CLINICAL FEATURES

Extensive differences exist in the pathological features, immunological status, treatment, and types of complications that develop with HD. The aim of HD classification is to define zones in the spectrum of the disease in which these features are similar or different.

Two systems of classification are now in general use: the Ridley-Jopling five-group classification and the WHO two-group classification (see Table 1).

Table 1. The HD spectrum as defined by the Ridley-Jopling and the WHO classifications.

Classification	Zones of the HD spectrum	
Ridley-Jopling	TT BT	BB BL LL
WHO Classification	Paucibacillary	Multibacillary

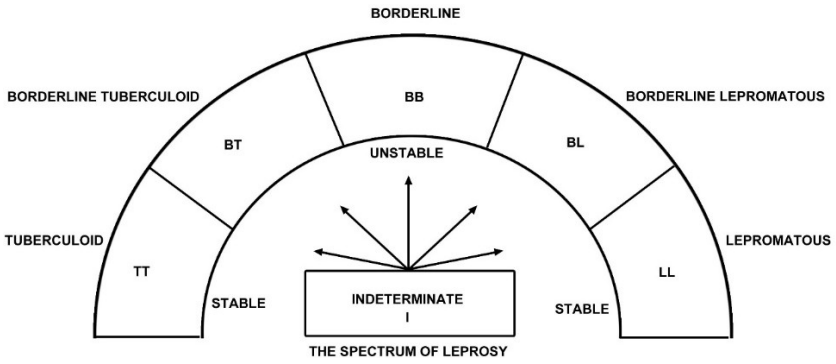
Ridley-Jopling Classification System: The Clinical Spectrum of Hansen's disease

Clinical features of HD cover a wide range, from a single hypopigmented skin macule to generalized disease. The Ridley-Jopling system captures this spectrum in 5 main classifications. The NHDP uses skin biopsy results and the Ridley-Jopling scale to determinethe classification for diagnosis and treatment. (Figure 1) The indeterminate class of HD willbe described in section C.

The World Health Organization (WHO) Classification System

When the WHO introduced Multidrug Therapy (MDT), they recommended a simplified classification for treatment purposes with only two categories, Paucibacillary (PB) and Multibacillary (MB). The current WHO definition of MB disease is "a case of leprosy with more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions." PB disease is a "case of leprosy with 1–5 skin lesions, without demonstrated presence of bacilli in a skin smear" https://www.who.int/news-room/fact-sheets/detail/leprosy.

Figure 1



Tuberculoid (TT)

Tuberculoid HD is characterized by limited disease with the presence of a few, well- defined hypopigmented skin lesions with marked sensory loss. Loss of hair in the lesionis common and there is often central healing. In the absence of treatment, the lesions enlarge slowly. This type of HD may be self-healing. (Figure 2)

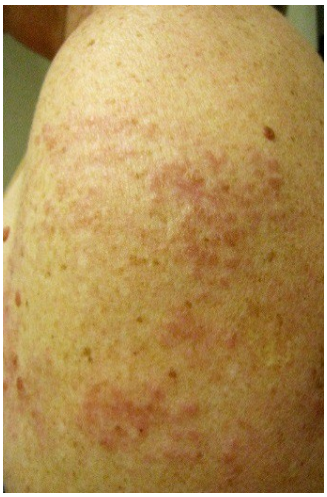


Figure 2

Histologically TT lesions reveal a very well-organized epithelioid granuloma, with dense foci of lymphocytes. *M. leprae* are rare and hard to find in biopsies. Caseation can occurin nerves (Figure 11).

Borderline Tuberculoid (BT)

When cellular immunity is high, but not as strong as TT, skin lesions look like TT lesions, but there are too many for the disease to be classified as polar TT. Patients with BT may have more than six skin lesions with very few bacilli.

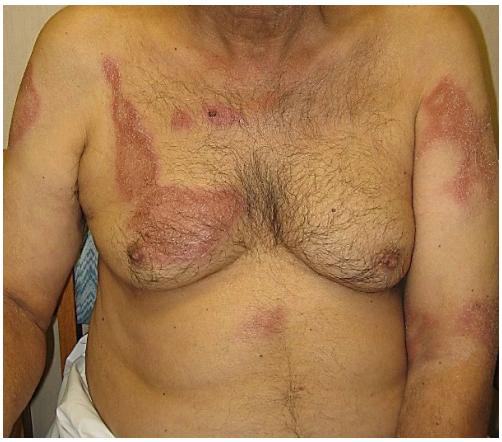


Figure 3

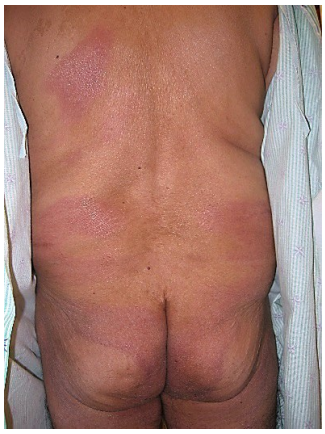


Figure 4

Histologically, BT lesions also show granulomatous inflammation, but not as compactly organized as TT. *M. leprae* is present in low numbers (Figure 11).

Mid-borderline (BB)

In BB, the lesions show a mixed appearance: some look like BT and others like BL lesions. Usually, BB lesions have very clearly defined areas of central healing ("punched-out" areas) with somewhat less well-defined outer edges.

This is a unique characteristic of BB HD, which is considered an immunologically unstable form where such patients tend to shift clinically toward BT or Borderline Lepromatous (BL). (Figure 5)

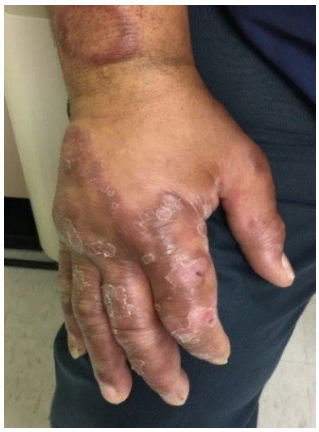


Figure 5

Histologically, BB lesions contain poorly organized granulomas as well as collections of foamy histiocytes. The acid-fast bacilli (AFB) seen are not numerous but are not difficult to find (see Figure 11 for an example).

Borderline Lepromatous (BL)

When cellular immunity is lower, skin lesions look more like Lepromatous (LL) lesions with macules and nodules more sharply defined than in polar LL, and with areas of normal looking skin between them. There is usually some asymmetry of the lesions, whereas in polar LL, they are symmetrical. (Figures 6 and 7).

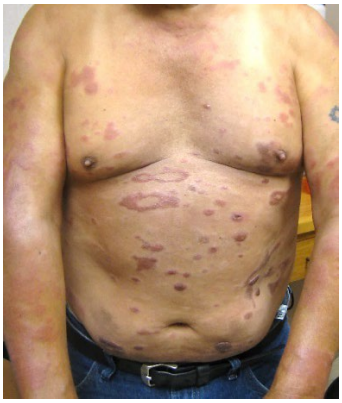


Figure 6

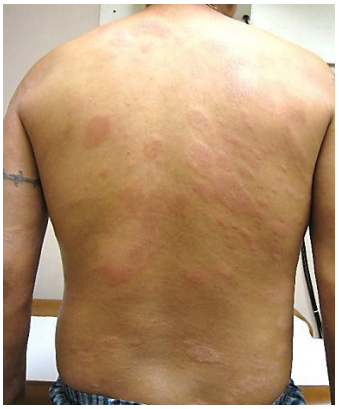


Figure7

Histologically, BL lesions reveal poorly organized collections of foamy macrophages anda substantial lymphocytic component. AFB are present in moderate to large numbers and are seen in almost every field and may include clumps called ‘globi’ (Figure 11).

Lepromatous (LL)

Lepromatous HD represents the extreme end of the spectrum where the patient essentially has no cell-mediated immunity to the infection and the bacilli multiply uncontrollably. The highest concentrations of bacilli are found in the skin and nerves. There may be bacteremia, even though the patient seldom feels ill. The skin lesions are numerous and may have vague margins. They may present as slightly hypopigmented macules, while in other cases the lesions may present as painless nodules or plaques. There is usually little or no loss of sensation in the skin in the early lesions. There is a generalized infiltration of the skin, usually maximized in the cooler zones of the body such as the extremities or the eyebrows. Extensive anesthesia can develop, but motor nerve function is often well preserved. (Figures 8, 9, 10).a

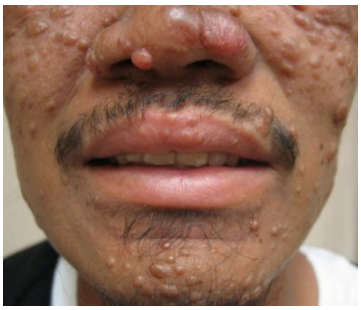


Figure 8

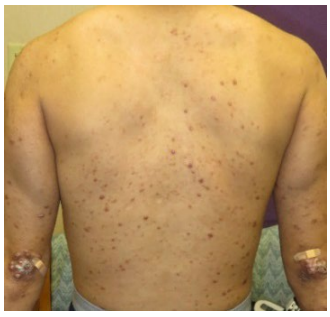


Figure 9

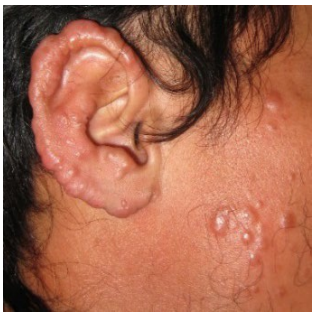


Figure 10

The histological appearance in LL includes totally disorganized collections of foamy histiocytes with a small component of lymphocytes. AFB are present in very large numbers, often with many globi. Bacilli are found in large numbers in nasal mucous membranes, and may be seen in the liver, spleen, lymph nodes, testes, eyes, smoothmuscle, and blood vessel walls (Figure 11).

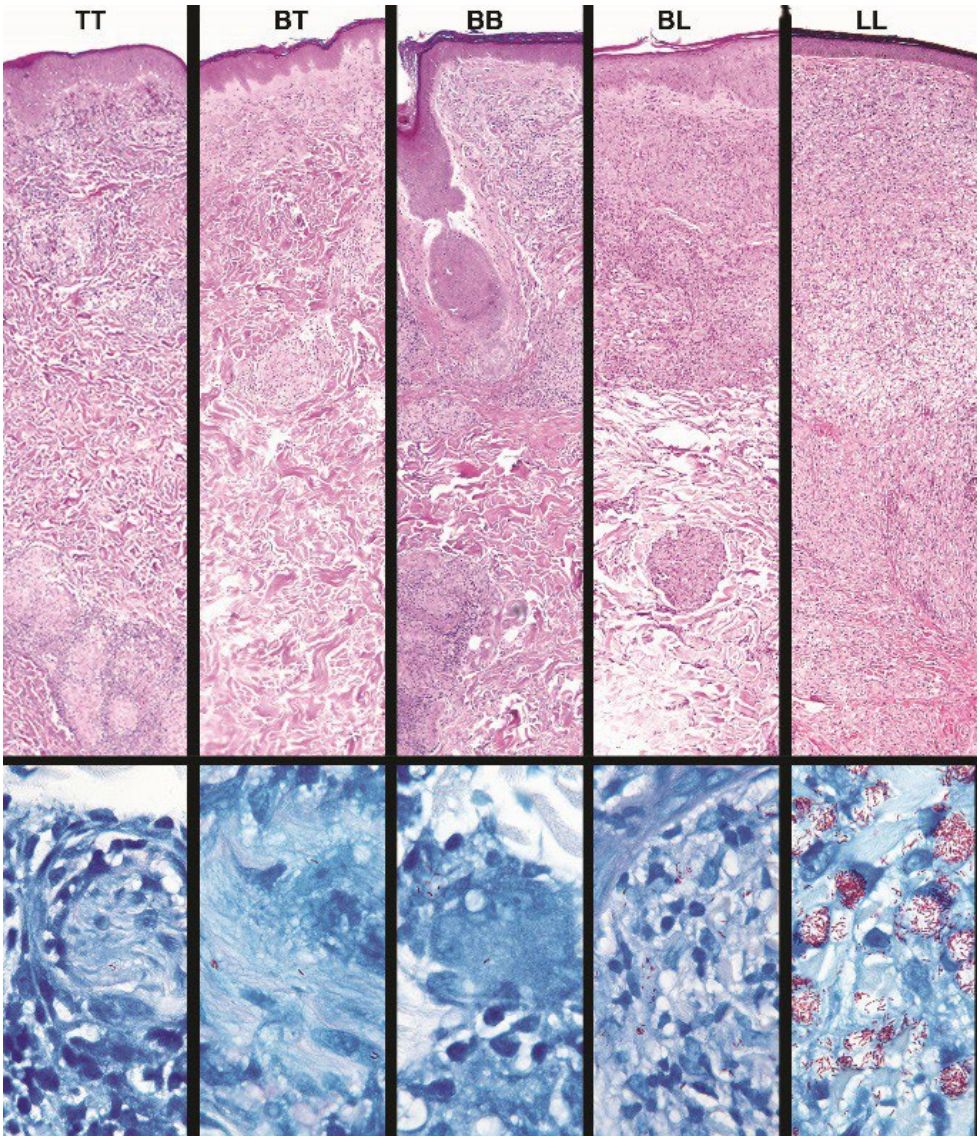


Figure 11 The histological spectrum of HD based on the Ridley-Jopling classification system.

Reprinted with permission from D. M. Scollard, L. B. Adams, T.P. Gillis, J. L. Krahenbuhl, R. W. Truman, and D. L Williams, The Continuing Challenges of Leprosy. Clinical Microbiology Reviews, April 2006 19 (2): 338- 381. doi:10.1128/CMR.19.2.338-381.2006

Other Types of HD

Other types of HD are sufficiently distinctive to merit a separate description, although there are varieties of the established groups of HD.

Pure neural HD

This type of HD is more common in endemic countries than in the U.S. In pure neural HD, one or more nerve trunks are affected and/or enlarged, but no skin lesions are visible. Diagnosis of pure neural HD is extremely difficult and sural nerve biopsies could be positive for *M. leprae* in less than 50% of cases (Shukla Et al., 2020).

Indeterminate (I)

There is also an indeterminate form of HD. This is the very earliest stage of the disease in which histological features are insufficient to make a definitive classification. Clinically, the lesions consist of one or two vague hypopigmented macules, which may be slightly dry in texture, sweat less than usual, and have minimally impaired sensation. It is difficult to find acid fast bacilli in the lesion. If it progresses beyond the indeterminate stage, it develops into one of the established forms of HD.

Diffuse Lepromatous Leprosy (DLL)

Diffuse infiltration of the skin over most of the body, with a smooth shiny appearance and extensive loss of body hair, including eyebrows and eyelashes. Some of these patients may develop a severe type of reaction known as Lucio's phenomenon, which involves diffuse ulcerations of the skin.

Some patients with confirmed infection of *M. lepromatosis* by PCR studies can exhibit an aggressive form of HD. Such patients develop multiple skin ulcers and necrotic skin lesions, which can be a challenge to treat.

Intensive wound management and aggressive treatment of reactions are necessary for the successful treatment of these patients. Patients often need inpatient specialized care.

Nerve Involvement in Hansen's Disease

Select Nerve Damage

Damage to select cranial and peripheral nerves is the basis of serious HD complications that can lead to permanent nerve damage and subsequent deformity and disability.

M. leprae and M. lepromatosis bacilli prefer cooler temperatures. The peripheral nerves are susceptible to infection at sites where the nerves are nearer to the surface of the skin. When the bacteria enter the nerve, inflammation, enlargement and demyelination can occur and lead to permanent nerve damage including sensory loss, muscle paralysis, and sweat gland dysfunction. The vulnerable sites and resulting deformities are shown in Figure 12.

M. leprae and M. lepromatosis bacilli can infiltrate the facial and trigeminal cranial nerves. Damage to the facial nerve can cause muscle paralysis leading to lagophthalmos, while damage to the trigeminal nerve may result in loss of corneal sensation. If untreated, this nerve damage can lead to blindness.

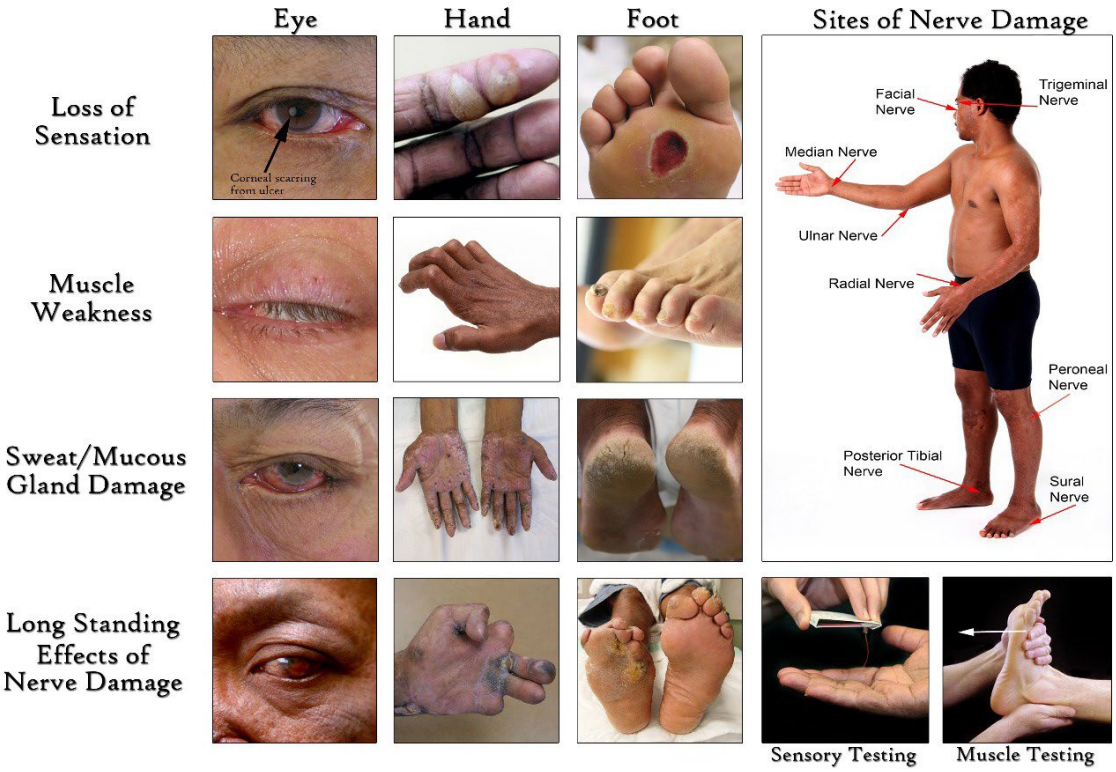


Figure 12

Neuropathy

Neuropathy can have early onset without any overt signs or symptoms. Some patients develop progressive sensory and/or motor loss in hands or feet and may complain of paresthesias (tingling, burning, stabbing sensation). These patients need to be assessed to determine that they are receiving appropriate antibiotic and immunomodulator treatment to prevent deterioration. If the loss has been present for greater than six months, the chance of recovery is diminished. Therefore, it is important to regularly monitor all patients under treatment for any changes in nerve function and treat accordingly.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis of Hansen's Disease

Identifying these cardinal signs of leprosy can be useful in making a clinical diagnosis.

1. Skin Lesions with Hypoesthesia and Anesthesia

Depending on the clinical form, HD skin lesions may or may not be anesthetic. (Note: Pure neural leprosy will not have skin lesions.)

2. Nerve enlargement

Enlarged and/or tender peripheral nerves are palpated at specific anatomical sites shown in Figures 15-21. More specific evaluation can be done using ultrasound or MRI of the affected nerve, especially, when no skin lesions are present in cases of pure neural leprosy.

3. Presence of Acid-Fast Bacilli

The only laboratory study that can definitively diagnose HD is a skin biopsy. There are no serologic or microbiological tests able to diagnose HD. *M. leprae* and *M. lepromatosis* are non-cultivable.

Polymerase chain reaction (PCR) tests for *M. leprae* and *M. lepromatosis* are available. NHDP can perform histopathology and PCR tests on skin biopsies (Baton Rouge, LA)

Differential Diagnosis of the Skin Lesions

HD skin lesions can mimic other skin diseases such as those listed below in Table 2.

Table 2. Mimickers of Leprosy Subtypes

Symptom	Type of HD	Differential Diagnosis
Hypopigmented patches	Indeterminate and Tuberculoid	Vitiligo, Pityriasis Alba, Post-inflammatory hypopigmentation
Erythematous macules/patches/plaques	Solitary/few for Tuberculoid or more for Borderline and Lepromatous	Psoriasis, Tinea Corporis, Nummular dermatitis, Syphilis, Mycosis Fungoides, Sarcoidosis
Annular Plaques	Mid-Borderline	Granuloma Annulare, Tinea Corporis, Psoriasis
Nodules	Borderline Lepromatous, and Lepromatous	Keloids, Dermatofibromas, Lymphoma, Metastases, Sarcoidosis, Other Mycobacterium, Deep Fungal Infections
Leonine Facies	Lepromatous Leprosy and Diffuse Lepromatous Leprosy	Paget's disease of bone, Mycosis fungoides, Polyostotic fibrous dysplasia, Amyloidosis, Lichen myxedematosus, Leishmaniasis, Lipoid proteinosis, Progressive nodular histiocytosis, Mastocytosis.

Table 3. Mimickers of Leprosy Reactions +/- ulceration

Reaction Type	Mimicker
Reversal Reaction (RR - Type I)	Cellulitis, Drug eruption, Lymphoma, Tumid Lupus, Sweets Syndrome
Erythema Nodosum Leprosum (ENL- Type II)	Erythema Nodosum, Sepsis, Panniculitides, Systemic Connective Tissue Disease flare

Mimickers of HD Neuropathy

Among the neurological conditions that may be confused with HD are:

- Heritable neuropathies
- Diabetic Polyneuropathy
- Entrapment neuropathy
- Cervicobrachial and scalenus syndromes
- Syringomyelia
- Amyloidosis
- Neurofibroma
- CIDP – chronic inflammatory demyelinating polyneuropathy

Important points to remember:

- HD never causes upper motor neuron lesions or involves the central nervous system. Proximal muscles are rarely involved.
- Sensory loss in HD is more common peripherally. There may be islands of preserved sensation on the hands or feet.
- The tendon reflexes are preserved, and proprioception is usually intact.

http://www.internationaltextbookofleprosy.org/chapter/differential-diagnosis- leprosy

See the website cited above for a more thorough discussion of the differential diagnosis of HD.

PSYCHOSOCIAL CONSIDERATIONS

The healthcare provider who first informs a patient about a diagnosis of HD sets the tone, which will convey either hope or fear. Fear increases the patient's anxiety and perpetuates the stigma and misunderstandings about HD. Even if the medical provider does not have experience in treating HD, he/she should convey that medical resources are available for this disease and that the patient can be treated and cured. Acceptance of the patient by all clinical staff is vital since it helps the patient feel confident that HD is like other treatable diseases.

By addressing the issues associated with stigma early during treatment, medical providers can decrease the negative effect on the patient. Moreover, by continuing to address the issue throughout treatment, the provider decreases the likelihood that patients will define themselves as leprosy patients for the rest of their lives.

The way in which patients view their lives and conceptualize the disease are decisive factors for their future mental health. Cultural background should also be considered. Various cultures have differing belief systems that can affect stigma, treatment, and compliance. Adherence to the National Standards for Culturally and Linguistically Appropriate Services (CLAS) is vital when caring for patients.

People diagnosed with HD find that stigma can manifest itself in prejudice, discrimination, and emotional distress. Educational efforts begin with the patient and medical provider and extend to the family and community. The goal of all interventions associated with HD is that the patient can maintain or reclaim physical, mental, and social well-being.

Stigma/myths

The stigma surrounding HD can be more damaging and enduring than the effect of the infection. Though HD is a treatable bacterial infection, the magnitude of the stigma can affect the patient's physical status, mental health, and interpersonal relationships.

Demystifying HD is an essential intervention to help the patient cope with HD and its stigma. In the early stages of educating patients about the medical aspects of HD, it is important to emphasize that it is treatable and curable.

Living with the diagnosis

Personal concerns arise for all patients as they interact with the people in their lives:

- Whom to tell?
- What to tell?
- When to tell others?

Signs of deformity, skin rashes, or reaction may force patients to deal with these questions sooner than they had hoped. Medical providers can help a patient decide what works best in his/her situation. Information should be given to patients about treatment resources for HD and support resources for coping with the disease, treatment, and stigma.

Common concerns and questions:

Initial reactions to a diagnosis of HD include:

- **Disbelief –** unaware that leprosy still exists.
- **Confusion –** wondering how and when they caught HD and if it is treatable.
- **Fear of contagion –** concern about "spreading HD" to family and friends.
- **Fear of rejection and social isolation –** often associated with images from the Bible, movies, etc. wondering if their appearance will change, if deformities are inevitable.
- **Feelings of shame** – associated with religious/cultural connotations of punishment, being cursed.
- **Feelings of depression or despair** – thinking their life as they knew it, is over.

Family members and others significant in the patient's life are likely to have the same reactions, fears and misconceptions. Providing the same education and support to them (with the patient's permission) helps not only the family and significant others, but also thepatient.

Psychiatric and Substance abuse disorders

This disease carries several psychosocial issues, which lead to a higher prevalenceof psychiatric disorders and substance abuse among patients with HD than in the general population.

Depression is the most common disorder found in HD patients. Early detection and treatment of psychiatric disorders is a powerful psychotherapeutic measure. Integrated behavioral healthcare improves outcomes.

The use of evidence-based screenings are helpful tools in detecting psychiatric and substance abuse disorders. Please see list of recommended of screening tools below. Please refer to our website for the screening tool forms and instructions.

1. Patient Health Questionnaire (PHQ-9) -Depression Screener
2. GAD-7 – General Anxiety Disorder Screener
3. PC-PTSD 5 - Post Traumatic Stress Disorder Screener
4. The Alcohol Use Disorders Identification Test: Self Report Version
5. Drug Abuse Screening Test (DAST 10)
6. HITS Domestic Violence Tool
7. Social Determinants of Health Screening Tool
8. SARI Stigma Scale – Screens specifically for stigma associated with HD diagnosis

CLINICAL EVALUATION

Patient Interview

1. Do you have the following symptoms?
    a. No pain with injuries such as cuts or burns.
    b. Wounds or ulcers that will not heal.
    c. Skin rash that has not responded to conventional treatment.
    d. Recurrent nosebleeds.
    e. Chronic nasal congestion.
    f. Burning sensation or loss of sensation on the hands or feet.
    g. Painful or tender peripheral nerves.
    h. Eye problems (pain, blurred vision, red sclera, poor blink reflex, corneal ulcers, lagophthalmos).
    i. Hair loss in areas of the body, especially the eyebrows and eyelashes.
    j. Fever, joint pain, malaise.
    k. Enlarged lymph nodes.
    l. Testicular pain or enlargement.

2. When did the symptoms first appear and how have they progressed over time?
3. Have you already sought treatment for these symptoms and where?
4. Were you initially diagnosed with a different disease?
5. Does anyone in the family have skin lesions?
6. What is your travel history?

Examination of the Patient

Every patient with suspected HD should have a careful examination of all skin (head to toes) and its appendages (hair and sweat/oil gland activity), eyes, nose, ears, neck, extremities, chest, abdomen, back, testes, and lymph nodes. The main goal of the examination is to confirm orexclude the cardinal signs listed above (Section VI-A).

Skin:

It is important to perform a complete examination of the skin in good light. Hypo-pigmented or hyper-pigmented flat or raised lesions may be found on the face, ears,trunk, extremities, buttocks, or thighs. Absence of sweating, hair loss, or changes in texture of the skin may also be present.

During an initial screening, any suspected skin lesion should be examined for light touch such as a tissue or similar item, and temperature discriminant with stainless steel or a mental part from a stethoscope. Skin lesions may manifest as macules, papules and/or nodules. There may be skin ulcers, tender red nodules, and edema of the face, ears, andextremities. Also, examine for loss of eyebrows and eyelashes (madarosis), dry, and fissured skin.

Eyes: Eye Screen Form

M. leprae and *M. lepromatosis* may cause inflammation and can result in episcleritis, scleritis and/or iridocyclitis.

Facial Nerve (VII Cranial Nerve):

The Facial Nerve innervates the orbicularis oculi muscles surrounding the eye. Paralysis causes lagophthalmos and subsequent corneal exposure resulting inhigh risk for injury and blindness. Damage to the seventh cranial nerve can also cause facial deformities due to muscle paresis or paralysis. Patients with facial lesions may be prone to facial nerve paralysis.

Trigeminal Nerve (5th Cranial Nerve):

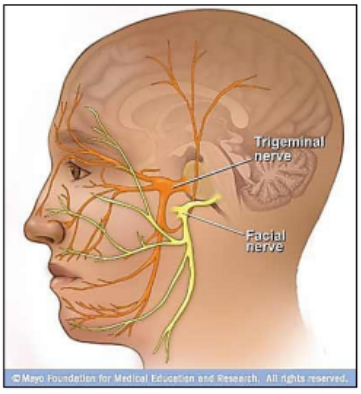


Figure 13. Facial & Trigeminal Nerves

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The sensory distribution of the 5th cranial nerve includes the cornea of the eye. The lack of protective sensation causes diminished or absence of the corneal reflex, resulting in corneal scarring, and raises risk of eye injury and blindness.

All HD patients should have a visual acuity exam, a simple evaluation for lid closure and evaluation for any evidence of redness or eye pain. This simple examination can prevent blindness. Any abnormal findings should prompt an ophthalmology consultation.

Nose

Look for signs of erosive rhinitis, nasal depression ("saddle nose" deformity), and nasal septum perforation. Inquire about nose bleeds (Figure 14)

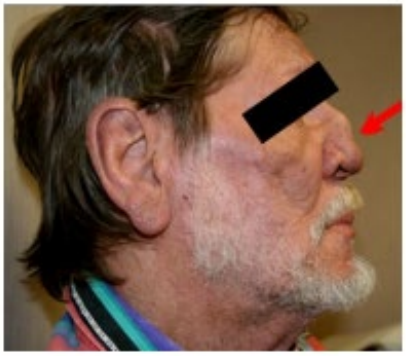


Figure 14. Saddle Nose

Neck: Great Auricular Nerve:

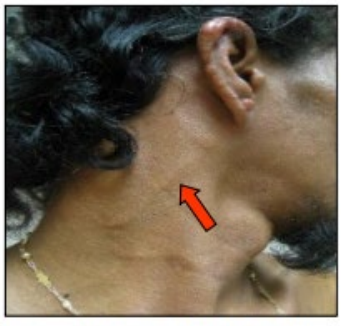


Figure 15. Great Auricular Nerve

Visualize and palpate the nerve located posterior to and over the sternocleidomastoid muscle. It may be enlarged but there is no significant consequence for motor or sensory damage.(Figure 15)

Extremities:

Upper Extremity

The NHDP Hand Screen is designed to identify nerve damage from HD. The hand screen is recommended at time of diagnosis for a baseline status, and on a routine basis to monitor the nerve status of the upper extremity for changes.
Evaluation includes sensory testing, muscle testing, skin integrity, nerve palpation, and identification of deformity. Inflamed nerves are at risk of damage causing secondary problems including sensory and motor deficits. The nerves commonly affected are located at sites in the upper extremities where they are superficial and easy to palpate. Palpation of the upper extremity nerves affected by HD is shown in Figures 16-18.

1. Ulnar Nerve located proximal to the cubital tunnel of theelbow.
Motor function- intrinsic muscles of the hand-weakness or paralysis can cause clawing of the 4th and 5th digits and a weak pinch.
Sensory distribution medial palm of the hand and 4th-5th digits.

Figure 16. Ulnar Nerve

2. Median Nerve located proximal to the wrist at the carpaltunnel.
Motor function- intrinsic muscles of the hand-weakness or paralysis can cause weak or absent opposition of thumb and clawing of the 2nd and 3rd digits ofthe hand. Symptoms may resemble carpal tunnel syndrome with numbness and tingling.
Sensory distribution- lateral palm of the hand, 1st, 2nd and 3rd digits.

Figure 17. Median Nerve

3. Radial Nerve located proximal to the anatomical snuffboxon the dorsum of the wrist.

Motor function- wrist and finger extensors-weakness can cause decreased wrist and digit extension and paralysis can cause wrist drop.

Sensory distribution- the dorsum of the thumb and dorsum of the hand proximal to the PIP joints of the 1st, 2nd, and 3rd digits.

Figure 18. Radial Cutaneous Nerve

Lower Extremity

The NHDP foot screen is designed to identify nerve damage from HD. The foot screen is recommended at time of diagnosis to establish a baseline status, and on a routine basis, to monitor the nerve status for early changes.
Evaluation includes sensory testing, muscle testing, skin integrity, nerve palpation, and identification of deformity. Nerves of the lower extremity affected by HD include (Figures 19-21):

1. **Peroneal Nerve –**
Located posterior/distal to the fibular head at lateral knee.
Motor function – anterior tibialis- dorsiflexion of the foot - paralysis can cause drop foot.
Sensory distribution – dorsum of the foot.

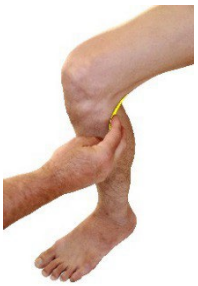


Figure 19. Peroneal Nerve

2. **Posterior Tibial Nerve**
Located at the tarsal tunnel posterior to the medial malleolus.
Motor function – Intrinsic muscles of the foot – paralysis can cause claw toes.
Sensory distribution – plantar foot.

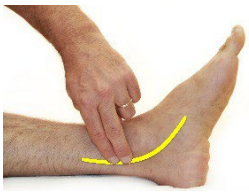


Figure. 20. Posterior Tibial Nerve

3. **Sural Nerve**
Located posterior and proximal to lateral malleolus.
Motor function – no motor component.
Sensory distribution– lateral foot.

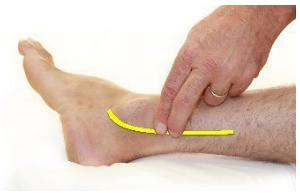


Figure 21. Sural Nerve

Joints and Tendons

Arthritis and tenosynovitis can occur during immunological reactions in borderline lepromatous (BL) and lepromatous leprosy (LL).

Breasts

In males, gynecomastia is a long-term sequela due to testosterone deficiency secondary to testicular involvement of HD.

Testicles

Direct invasion of the testicles probably occurs in many cases of Borderline Lepromatous and Lepromatous disease. The testicles are a cool part of the body and are preferentially affected. Assessment: Ask male patients about pain or swelling of the testicles. Swelling and pain may occur during immunological reactions.

Lymph nodes

Tender lymph nodes may be seen with ENL reaction.

Laboratory Studies

Skin Biopsy

A skin biopsy is a confirmatory laboratory test for Hansen's disease.

PCR Assay (Polymerase Chain Reaction)

At NHDP, PCR assays can be ordered.

Slit Skin Smears

For reliable results, slit skin smears need to be performed by a properly trained laboratory technician. Results of Fite stained skin smears gives the clinician an assessment of the range and severity of the patient's infection as they help assess a need for continuation of anti-inflammatory treatment if patients continue to experience immunological reactions.

Special Considerations

HD and Pregnancy:

A pregnant female with HD is uncommon in the U.S., but a few cases occur each year. Most of these pregnancies are uneventful as far as HD is concerned, but there are potential problems and risks that should be considered when advising female HD patients of childbearing age, and when managing pregnant patients who have HD. ***Pregnancy should not delay treatment of the infection.***

All female patients of childbearing age should be advised to postpone pregnancy until MDT has been completed. It is especially important for patients who have evidence of reaction or neuritis, since these problems can be exacerbated during pregnancy, and in the postpartum period.

Alterations in the immune response during pregnancy can cause suppression of the cell-mediated immune (CMI) system, and its recovery in the postpartum period appears to play a role in the clinical manifestations of HD in women. It is not uncommon for the first symptom of HD in women of childbearing age to occur during pregnancy or in the postpartum period.

ENL is more common during pregnancy when the CMI is depressed, while reversal reactions are more common during the postpartum period when the CMI is recovering. The risk of reactions or neuritis during pregnancy will vary considerably with the type of disease and the amount of treatment a patient has received prior to the pregnancy. If a reaction occurs during pregnancy, consider consultation with NHDP.

HD and Children:

HD in children is rare in the US and may have an atypical presentation. Management of the disease should be handled by a pediatric specialist and in consultation with NHDP. Transmission of HD to children or adults usually does not occur after the patient starts on treatment. Preventive treatment for close contacts needs to be discussed with the provider.

Testicular HD:

Direct invasion of the testicles probably occurs in many cases of Borderline Lepromatous and Lepromatous disease. The testicles are a cool part of the body and are preferentially affected. In males <40 years old, with lepromatous leprosy, consider testing for testosterone levels and warn patients about immunological reactions causing painful enlargement of the testicles.

HD Surveillance Form

The HD Surveillance Form is the document used to report leprosy cases to the US NHDP registry. The surveillance form is only required one time, when a patient has been newly diagnosed. **Reporting the HD Surveillance Form to the NHDP does not replace state reporting requirements**. Please refer to your state's health department for specifics of HD reporting.

Follow-Up Visit

- Patient Interview
- Examination of the patient
- Laboratory monitoring (See Lab Monitoring schedule – Table 5)
- Annual biopsy and skin smears are optional.
- Eye, Hand and Foot Screens (See Frequency of Performance in Section XVI)
- Patient Education every clinic visit

TREATMENT OF HANSEN'S DISEASE

While the care of an individual diagnosed with HD involves considerably more than prescribing medication, the appropriate drug combination is the most important step toward curing the infection. Health care providers should emphasize to their patients the importance of taking all medications for the duration of treatment. This section will providean overview of the medications used to treat HD, potential side effects, and alternative medications.

NHDP recognizes that there are multiple treatment options for HD. The following options include the treatment regimen that NHDP utilizes as well as other treatment options used by different programs throughout the world. It is recommended that each provider tailor the treatment option based on the patient's unique disease characteristics and needs. Read package inserts for complete information regarding each medication and contact the NHDP for questions not answered in the material below.

Chemotherapy: The Anti-Leprosy Drugs

Rifampin

Rifampin is available as a 150 mg and 300 mg reddish capsule that is bactericidal. Rifampin is absorbed best when taken on an empty stomach, 1 hour before eating or 2 hours after eating.

Side Effects: Elevated liver function tests (especially ALT, AST). Rifampin should be discontinued if the ALT or AST rises to more than 2.5x normal. Rifampin enhances the toxicity of alcohol. Occasionally patients will develop thrombocytopenia and therefore platelet counts should be monitored.

Patients must be advised that urine and other bodily fluids will turn a reddish color.

Interactions: Rifampin is a strong inducer of liver enzymes. There are several drug interactions with rifampin including steroids, oral contraceptives, warfarin, and dapsone among many others. Monthly dosing minimizes these interactions.

Moxifloxacin

Moxifloxacin is a fluoroquinolone antibiotic that is bactericidal. It is available as a 400mg tablet which should be given once a month.

Side Effects: Fluoroquinolone antibiotics including moxifloxacin have been associated with tendonitis, tendon rupture, and QT interval prolongation. Monthly dosing lessens the likelihood of these adverse effects, but patients should be monitored.

Interactions: Avoid co-administration of moxifloxacin with products containing divalent cations such as iron, magnesium, zinc, calcium, and aluminum. Do not take moxifloxacin within 2 hours of consuming milk, yogurt, calcium-fortified juices, vitamin supplements, antacids, and certain laxatives.

Minocycline

Minocycline is a tetracycline antibiotic that is bactericidal and lipophilic. Minocycline is available in 100mg tablets or capsules.

Side effects: Minocycline can cause hyperpigmentation, but this effect is not as likely when taken monthly. Minocycline causes photosensitivity, and the use of sunscreen is recommended.

Interactions: Avoid co-administration of minocycline with products containing divalent cations such as iron, magnesium, zinc, calcium, and aluminum. Do not take minocycline within 2 hours of consuming milk, yogurt, calcium-fortified juices, vitamin supplements, antacids, and certain laxatives.

Minocycline is not to be used during pregnancy.

Dapsone

Dapsone is bacteriostatic and therefore, must be used in combination with other antibiotics. Dapsone monotherapy may cause drug resistance. Dapsone is available in 25 and 100 mg white tablets. The normal dose is 50 mg or 100 mg daily with or without food.

Side Effects: Mild hemolytic anemia is common. Patients who have a glucose-6-phosphate dehydrogenase deficiency cannot take dapsone and will need an alternate drug. Rare cases of agranulocytosis have been reported.

Dapsone allergy is rare, but if it occurs, it could be mistaken as an HD reaction. Severe cases may develop dermatitis, fever, hepatitis, or even Stevens-Johnson syndrome.

An alternative to dapsone therapy because of intolerance, anemia, methemoglobinemia, or G6PD deficiency is clarithromycin XL 500mg.

Clofazimine

Clofazimine is a lipophilic dye that has antibacterial and anti-inflammatory properties. It is available as a brown 50 mg gelatin capsule. The serum half-life of the drug is about 10 days, and the tissue half-life may be up to 70 days. The current antibacterial doseis 50 mg daily with fatty food.

Side Effects: Clofazimine gives the skin a red to blue/black discoloration, more marked in HD skin lesions than in unaffected skin. Sun exposure intensifies the discoloration. The color takes several weeks to develop and may take years to disappear after the drug is discontinued. NOTE: Some patients are so distressed by the discoloration that they discontinue the medication without informing the physician. It is important, therefore, to alert the patient in advance that this is a possible side effect. Other side effects include dryness and itching of the skin and eyes.

QT prolongation, crystallization in mucous membranes

Special acquisition requirements:

Clofazimine, used for decades to treat HD around the world, is no longer available in the US commercially. The only way to obtain the drug in the U.S. is by completing an investigational new drug (IND) application through the Food & Drug Administration (FDA). Please contact the NHDP for further information.

National Hansen's Disease Programs
9181 Interline Avenue, Baton Rouge, LA 70809
Email: HRSANHDPCLINIC@hrsa.gov
Phone: 1-800-642-2477
Fax: (225) 906-5277

Alternative Anti-Microbial Agents

The main indication for the use of alternative anti-microbial agents is intolerance for the recommended drugs or drug-drug interaction.

Clarithromycin XL, 500 mg is also effective against HD and can be used as a substitute for any of the other drugs in a multiple drug regimen.

Levofloxacin, 500 mg monthly, is also effective against HD and can be used as a substitute for any of the other drugs in a multiple drug regimen. Not all fluoroquinolones are effective against *M. leprae*. Only moxifloxacin, levofloxacin, or ofloxacin should be used.

Protocols

The former NHDP regimen with daily rifampin is no longer recommended due to significant drug-drug interactions, that is in line with WHO recommendation that uses monthly doses.

The WHO recommends multi drug therapy of dapsone, rifampicin, and clofazimine with different lengths of treatment. More information about the WHO treatment regimen can be located at [WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy]

Table 4

HANSEN'S DISEASE MONTHLY ANTIBIOTICS (RMM) DOSING INSTRUCTIONS

RMM = RIFAMPIN, MOXIFLOXACIN, MINOCYCLINE

MONTHLY TRIPLE ANTIBIOTIC REGIMEN (RMM)				
Leprosy Type	**Rifampin**	**Moxifloxacin**	**Minocycline**	**Length of TX**
Paucibacillary (TT, BT, IN)	600 mg	400 mg	100mg	Once a month for 12 months
Multibacillary (LL, BL, BB)	600 mg	400mg	100mg	Once a month for 24 months

Each monthly dose of RMM consists of two rifampin 300mg capsules, one moxifloxacin 400mg tablet, and one minocycline 100mg tablet. All 3 antibiotics should be taken once a month on the same day. The three antibiotics can be taken all at once but are better tolerated when each is taken at least 15 to 45 minutes apart. Some patients prefer to space out the antibiotics with breakfast, lunch, and dinner to prevent GI side effects. This is also acceptable so long as all 3 antibiotics are taken on the same day.

Rifampin will cause a temporary reddish/orange discoloration of urine and bodily fluids. Do not drink alcohol when taking rifampin.

Moxifloxacin and minocycline should not be taken at the same time as multivitamins or antacids. Any supplements containing iron, magnesium, zinc, calcium or aluminum should be taken at least 4 hours after monthly antibiotics have been taken.

Special Considerations

Treatment for Pregnant Women:

While pregnancy during HD treatment is strongly discouraged, it occurs, consult with NHDP to determine medical management.

Treatment for Children:

HD in children is rare in the US and may have an atypical presentation. Management of the disease should be handled by a pediatric specialist and in consultation with NHDP.

Testicular HD

Testicular function may be affected by HD. Check testosterone level at baseline for multibacillary HD male patients < 40 years old. If testicular function is diminished by HD, testosterone replacement should be considered.

Laboratory Monitoring

Table 5 Laboratory Monitoring for Drugs Used to Treat Hansen's Disease

Drug	Laboratory Studies	Every 3 Months if stable
Initial studies for all drugs	CBC w/platelets, CMP, CRP, Sed rate, vit. D level, HBsAg, HCV Ab, QuantiFERON-TB Gold	CBC w/diff, CMP, CRP, Sed rate, vit. D level

*Drugs used in managing reactions (see below Section X -Immunological Reactions)

Prognosis

Patient isolation is unnecessary since HD is difficult to transmit to another person before treatment. Many patients can continue normal activities and occupations with little interruption in their daily routines during treatment.

The success of HD treatment is measured by completion of prescribed medication. Most patients in the U.S. have little or no disability at the time of diagnosis. If recent nerve damage or neuritis is present at diagnosis, prompt treatment may improve the patient's nerve status or at least prevent further damage to the nerves. While the prescribed multidrug regimen minimizes the possibility of nerve damage, 30-40% of patients have recurrent episodes of reaction during treatment with possible nerve damage. Unfortunately, nerves damaged for years prior to diagnosis will not recover, and disabilities are permanent.

Follow-Up after Completion of Treatment

Clinical examinations are performed at the following intervals after MDT is complete:

- Paucibacillary (PB) - Annually up to two years
- Multibacillary (MB) - Annually up to three years
- Annual follow-up forms are completed at each yearly follow-up visit.

- Skin biopsies are performed at the doctor's discretion.

  Patients with loss of protective sensation or history of hand and foot ulcers may need to be referred to appropriate providers for routine follow up care (providers: PT, OT, or podiatrist).

IMMUNOLOGICAL REACTIONS

The majority of HD patients will experience an acute hypersensitivity or immunological reaction to the *M. leprae* organism during the course of their disease.

Table 6 identifies the two types of reactions and how they correspond with the WHO/Ridley-Jopling classification. Table 7 includes a summary of the differences between reversal (Type I) and ENL (Type II) reactions. Unfortunately, there are no predictors to identify which patients will develop a reaction. Patients who do develop reactions should start immunomodulatory treatment and be monitored closely as they are at a higher risk of nerve damage and subsequent disabilities and deformities.

Table 6

<table>
<tr><th colspan="5">WHO and Ridley-Jopling classifications with corresponding Reaction types</th></tr>
<tr><td colspan="2">Paucibacillary (PB)</td><td colspan="3">Multibacillary (MB)</td></tr>
<tr><td>TT</td><td>BT</td><td>BB</td><td>BL</td><td>LL</td></tr>
<tr><td rowspan="2">No Reaction</td><td colspan="3">Reversal Reaction (RR)</td><td></td></tr>
<tr><td></td><td colspan="3">Erythema Nodosum Leprosum (ENL)</td></tr>
</table>

Unexperienced providers may have difficulty in classifying immunological reactions, particularly for patients in BL spectrum, where patients may have elements of both types of reactions.

Reversal Reaction (RR or Type 1 Reaction)

Reversal reaction is recognized by the development of edema and erythema in existing skin lesions. Severe cases are characterized by fever, edema of the hands and feet, and erythema of pre-existing skin lesions, which may ulcerate. Reversal reactions can also involve the nerves. Edema and granuloma formation may lead to sudden nerve damage, with swelling and pain in one or more of the commonly affected nerve trunks.

While reversal reaction generally occurs during the first 6-12 months of treatment, it may occur later, even after drug treatment is complete. Reversal reaction is also seen in untreated HD, and sometimes its onset is the event that makes the patient decide to seek medical attention.

If a patient remains untreated, the reaction might subside after a few weeks. However, a Type I reaction can also persist, with the lesions becoming more extensive.

A reversal reaction is an acute exacerbation of the normal cell mediated immune response to *M. leprae*. It is an example of delayed-type hypersensitivity causing clinical disease. While the precipitating event is unclear, it seems likely that the bacilli residing in Schwann cells are for some reason, suddenly "recognized" by the cell-mediated immune system. As a result, the patient's peripheral and dermal nerves are damaged or destroyed along with the bacilli.

Biopsy and pathology reports may show edema, epithelioid granuloma formation, and an influx of lymphocytes, but this is not diagnostic of Type I reaction.

Erythema Nodosum Leprosum (ENL or Type 2 Reaction)

ENL often appears as transient red nodules in the skin, which are often tender and painful. The nodules can appear on almost any part of the body, including the face, and will appear on previously normal skin. The nodules may resolve in 7-10 days, often leaving a characteristic mottled hyperpigmentation. Patients with ENL often have fever and experience a generalized illness. There may be associated attacks of painful neuritis, arthritis, lymphadenopathy, uveitis, and orchitis, though it is unusual for all of these to bepresent at the same time. Edema of extremities is common.

In severe cases of ENL, the patient may have hepatosplenomegaly, high fever and/or a clinical presentation that resembles Systemic Inflammatory Response Syndrome (SIRS). Skinnodules are usually present.

ENL may be episodic with frequent attacks. In some cases, these episodic attacks come so frequently that the reaction is considered continuous. In such cases, it often persists for 2 years or more.

ENL reactions cause new crops of nodules to appear, and edema of the hands and feet may develop. If left untreated, neuritis can produce extensive nerve damage.

ENL occurs in patients who have large amounts of circulating anti-mycobacterial antibodies and is proposed to be a clinical manifestation of antigen-antibody immune complex formation. The immune complexes are usually formed extravascularly in sites where *M. Leprae* are present in high concentration, such as skin, nerves, lymph nodes and testes.
These complexes elicit an inflammatory response, which results in the clinical manifestations of ENL. It also has been shown that tumor necrosis factor alpha is elevatedduring ENL and decreases as the reaction subsides. ENL occurs most commonly in patientswho are receiving MDT but can occur before treatment or long after treatment is completed. The antigen in this reaction is from dead *M. leprae* bacilli.

ENL reaction is characterized by foci of neutrophil infiltration with fragmented *M. leprae*and associated vasculitis. After a few days, as the lesion resolves, the neutrophils are replaced by loose collections of lymphocytes.

Table 7

Summary: Type 1 (Reversal Reaction) and Type 2 (ENL) Differences		
Type of reaction	**Type 1 (Reversal Reaction)**	**Type 2 (ENL)**
Mechanism	Cell-mediated; delayed hypersensitivity reaction	Antigen antibody (immune complex) reaction
Skin	Mild: - red, mildly swollen skin lesions - no lesions on the face - no edema hands, feet or face Severe: - painful, swollen skin lesions - ulceration/threatening ulceration of skin - swollen lesions on the face - edema of hands, feet, face	Mild: - minimal pain; no ulcerating skinlesions Severe: - red, painful, bullous, or ulcerating skinlesions common on the face, extensorsurfaces of arms and legs. - edema of hands and feet
Constitutional symptoms	Good. Little or no fever or other constitutional symptoms	Mild: - afebrile/only mild fever Severe: - febrile systemic illness
Other Organs/Tissues	Not affected	May be affected: Joints- arthritis Testes- orchitis Kidneys- proteinuria
Nerves	Mild: - no painful or tender nerves Severe: - nerves close to skin may be enlarged, tender, painful (neuritis) with loss of nerve function, i.e. diminished sensation, muscle weakness of hands/feet. - rapid onset	
Eyes	Mild: - no eye problems Severe: - weak eyelid muscles leading to incomplete closure (lagophthalmos) due tonerve damage - Internal eye disease (uveitis, scleritis)	

TREATMENT OF REACTIONS AND NEURITIS

Reactions are a major cause of nerve damage; subsequently the focus of management should be on preventing or minimizing nerve damage. Damage to the nerves is caused by inflammation within the nerve due to intraneural *M. leprae*, which is like the process seen in the skin. In untreated HD without reaction, nerve damage is more insidious, while in

reaction, nerves may be damaged within days. Skin reactions and acute neuritis often occur together. See Table 8 for a summary of treatment recommendations for reactions.

Treatment of Reversal Reaction (Type 1 Reaction)

Mild reaction

Mild reaction is characterized by the presence of edema and erythema of existing skin lesions only. There may be low-grade fever and some general discomfort. If there are any signs of neuritis such as nerve enlargement, pain, tenderness or loss of nerve function, the reaction is no longer considered mild and should be managed as a severe reaction. The treatment of mild reaction should be addressed immediately before it progresses. Patients must be observed closely for deterioration of nerve function which requires more aggressive treatment. Antibacterial treatment for HD should continue.

Severe reaction

Severe reaction is characterized by the presence of any of the following:

- Nerve pain and/or nerve function impairment (sensory or motor)
- Edema of the hands and/or feet
- Fever and systemic symptoms such as malaise
- Joint Pain
- Swollen and tender skin lesions: facial lesions indicate risk of facial nerve damage
- Ulceration of inflamed skin lesions

Prednisone

In severe reactions, an overactive immune response causes tissue damage; therefore, treatment involves anti-inflammatory medications with immune modulators.

Treatment must be individualized to the patient's needs. Factors to be considered are age, co-morbidities, and polypharmacy. The presence of facial lesions or foot drop should be treated immediately and aggressively as they pose the threat of permanent nerve damage and paralysis.

The initial dose of prednisone might be as high as 1mg/kg for 5 days or less in a single morning dose. Methotrexate (MTX) as steroid sparing must be initiated at the same time. Prednisone should be tapered to 5-10 mg within 2 weeks. It may be continued and further titrated down slowly over a period of 6-12 months, depending on the severity of the reaction and how the patient responds to treatment. The main objective is to provide relief of the patient's symptoms and prevent nerve damage.

If at any dosage level the clinical signs of reaction persist or recur, the doses of MTX and prednisone may be increased until the symptoms resolve, at which time, slow tapering of the dosage can begin again.

Rapid improvement of nerve function occurs most often in situations when the lesion is of recent onset (less than six months). On the other hand, regenerationand recovery of function following severe nerve damage will take many monthsor may not occur at all. Therefore, lack of nerve function improvement is not necessarily an indication to increase the dosage of prednisone or prolong the period of steroid treatment.

Clofazimine

In select cases, a trial of Clofazimine 200-300 mg daily for 6-12 months may be indicated to reduce/end steroid dependence. Clofazimine does not have a fast-acting anti-inflammatory effect. The patient may have to take it for 6 weeks or more to receive the full inflammatory effect.

Surgery

On a rare occasion, if a nerve trunk remains markedly enlarged and the patientcomplains of persistent nerve pain despite intensive steroid treatment, consider surgical consultation (See Section XIII on Surgical Interventions).

Treatment of Erythema Nodosum Leprosum (ENL - Type 2 Reaction)

The management of ENL will vary somewhat depending on whether the reaction is mild orsevere and whether it is intermittent or continuous. If the physician is inexperienced in treating this reaction, consider contacting NHDP at 1-800-642-2477 or email HRSANHDPCLINIC@HRSA.GOV

Mild reaction:

Mild reactions should be addressed immediately as in Type I reaction. Methotrexate should be considered in low doses as an anti-inflammatory/immune drug. Although not specific, C-reactive protein (CRP) may be used to monitor the severity of reactions.

Severe reaction:

These patients often present to the Emergency Room and are thought to be septic. Oneor more of the following are present:

- Fever and malaise
- Elevated white blood cell count
- Painful and ulcerating skin lesions
- Nerve pain and/or nerve tenderness with palpation
- Sudden loss of sensation or muscle weakness in hands, feet, or eyes.
- Edema of the hands and/or feet
- Joint pain
- Orchitis
- Red painful eye (Uveitis, Scleritis)
- Headaches

IV corticosteroids should be administered for 24 – 48 hours in the inpatient setting (Solumedrol 125mg every 8 hours). Again, initiating methotrexate is highly recommended. After the reaction is controlled, switch to oral prednisone, no higher than 40mg/daily, with taper by 5 mg every 1-2 weeks. Consider initiation of thalidomide therapy.

Thalidomide is the drug of choice for ENL. It is a TNF alpha inhibitor. Thalidomide is prescribed based on the severity of the symptoms with a starting dose can be 200 mg taken at bedtime as drowsiness is a side effect. Thalidomide is teratogenic causing severe birth defects if taken by women during pregnancy. Women of childbearing age must use two forms of birth control and take a monthly pregnancy test while on therapy. Thalidomide prescribing and distribution is tightly regulated by a Risk Evaluation and Mitigation Strategies (REMS) program. Information about enrolling in the REMS program, finding a specialty pharmacy, and patient assistance can be found on the Thalomid website.

Clofazimine can be given in a divided dose of 200 mg daily for several months, then reduced to 100 mg daily. The addition of clofazimine at these doses will usually make it possible to reduce the dose of steroids required, but not eliminate them entirely. Clofazimine is not quick acting, and it may take 6 weeks or more for the full effect on the reaction to be noted. Patients receiving larger doses of clofazimine willhave more skin pigmentation changes and possibly more frequent gastrointestinal side effects. When the patient has required no steroids for approximately three months, the dosage of Clofazimine can be reduced to 50 mg daily. If clofazimine is not required for antibacterial treatment, it can be discontinued when no steroids have been required for an additional three months.

Apremilast may be a useful drug in patients refractory to management with the drugs traditionally used for ENL management or for whom thalidomide would be considered inappropriate. There are several published case reports establishing the utility of this drug for management of refractory and recurrent ENL, however this is an off-label usage. Cost of the drug and insurance coverage are potential barriers to use.

Methotrexate dosed weekly is used as a steroid sparing agent. The dose can be titrated upward weekly. The maintenance dose is 15-25 mg once weekly. Patients should be closely monitored so that toxic side effects can be detected as early as possible. Baseline assessment should include CBC with differential and platelet count, hepatic enzymes, and renal function tests. These should be repeated every 1 to 2 months; if stable, then repeat every 3 months. It is recommended that 1 mg folic acid should be taken daily except on the day of the weeklydose. The medication should be stopped if mouth sores, or diarrhea develops. Methotrexate is contradicted in pregnancy.

Prior to starting methotrexate, or before restarting after a rest period, pre-treatment assessments should include:

- Full blood count including differential blood count and platelets
- Liver function tests including serum albumin
- Renal function tests
- Exclude Hepatitis B and C if clinically indicated
- Exclude TB if clinically indicated

Lucio's Phenomenon

Patients experiencing Lucio's Phenomenon are acutely ill. In addition to standard antibacterial treatment, these patients are treated similar to those with ENL using a high dose of clofazimine, steroids and thalidomide. Close attention should be given to skin ulcerations which can cover the extremities.

Patient Education Regarding Reactions

An important part of management of reactions is providing correct information and listening to the concerns of patients and their families. Patients usually fear that treatment has failed, their disease is getting worse, and they will suffer permanent disability and disfigurement. In chronic reactions, especially ENL, patients often become depressed. It should be emphasized that a reaction does not indicate a failure of antibacterial treatment or toxicity to drugs. Reactions are due to the immune system reacting to the dead bacteria. Patients can always be reassured that HD, and reactions are treatable conditions and that even long-standing reactions will eventually end. In most cases, the long-term prognosis is good and there should not be any further progression of nerve damage or disability after the initiation of treatment. Patients must understand that discontinuing medication is NOT a good option. Patients should contact their physician at the first sign of an ENL flare.

Table 8

Summary: Treatment of Reactions	
Reversal Reaction (Type 1)	
Mild Symptoms	Severe Symptoms
- erythematous, mildly swollen skin lesions - no painful or tender nerves - no lesions of the face - no edema of the face, hands or feet	- painful swollen skin lesions - ulceration or threatening ulceration of skin - swollen lesions of the face - edema of the hands, feet, or face - diminished sensation or muscle weakness in hands/feet
Treatment	Treatment
- low dose of methotrexate (7.5mg to 10mg/weekly) should be initiated for 6 months - low dose of prednisone 1mg to 2.5mg daily may be initially added for 3 months then reassess patient.	- High dose prednisone – 1mg/kg for 5 days then taper over 6 months - Methotrexate 15mg-20mg/weekly as a steroid sparing - Clofazimine – in selected cases, trial of 300 mg daily up to 3 months. If effective, continue at reduced dose 200 mg for 3 months, followed by 100 mg for additional 6 months
Erythema Nodosum Leprosum (Type 2)	
Mild Symptoms	Severe Symptoms
- afebrile or only mild fever - minimal pain and no ulcerating skin lesions - no painful or tender nerves - no eye problems	- febrile systemic illness - painful or ulcerating skin lesions - painful or tender nerves - diminished sensation or muscle weakness in hands or feet - edema of the hands and/or feet - uveitis, scleritis, arthritis, orchitis, proteinuria
Treatment	Treatment
- Treatment is the same as mild symptoms for Type 1.	- For inpatient setting: solumedrol 125mg IV every 8 hours for 48 hours then switch to oral - For outpatient setting: 1-1.5mg/kg prednisone for 3 -4 daily tapered to lowest dose required to control the reaction - Methotrexate: Initiate immediately 15mg – 20mg/weekly as a steroid sparing - Thalidomide is the drug of choice: 200 mg daily in divided doses, tapered to 100 mg daily within 2 weeks, then given 50-100 mg daily for as long as required to control the reaction, which can be 5 years or longer - Clofazimine- 200 mg daily for 6 months, then 100 mg daily for 1-2 years - Combinations of above regimens may be used.
During the prescribed time of treatment, hold all antibiotics during acute phase of reactions. Rifampin reduces the effectiveness of all steroids, including prednisone, so it is necessary to hold rifampin until patient is stable to obtain an optimal therapeutic response to prednisone. Another option is to increase prednisone on the day that rifampin is taken.	
A practical guide for the dose of prednisone in neuritis is that the initial doses should be large enough to relieve the pain and tenderness in the nerves in 24-48 hours. The maintenance dose should be large enough to prevent recurrence of nerve pain. An exception to this would be patients who have had long-standing neuritis with persistent pain probably due to scarring in and around nerves, but whose nerve function status has been stable for a long period. Prednisone is not usually beneficial in such patients.	

PREVENTION OF DISABILITY (POD)

Images of deformity and disability still prompt fear and stigma associated with leprosy (HD). Early diagnosis and treatment, before nerves are damaged, is the best prevention of the deformity and disability. If nerve damage has occurred, a long-term management program using a team approach is best practice. Routine care for insensitive eyes, hands and feet is crucial to minimize or prevent deformity. The POD team will include some or all the following professions: physician, nurse, occupational therapist, physical therapist, ophthalmologist, pedorthist, podiatrist, orthotist, social worker, case manager, surgeon, and pharmacist. Each member of this interdisciplinary team brings specific expertise that collectively provides comprehensive intervention. NHDP developed a five-step program that outlines the components of essential preventative care. The following are the fivecomponents of the NHDP POD Program.

Eye, Hand and Foot Screening

Baseline and routine evaluation of the eyes, hands and feet is foundational for objectively measuring the patient's nerve status. The goal of screening is to identify sensory loss, muscle weakness/paralysis, anatomical deformity, enlarged/tender nervesand autonomic dysfunction. During treatment with MDT, screens are performed quarterly to identify changes in peripheral nerve function. During reaction, screens maybe performed as often as monthly to detect early nerve changes for immediate treatment. Based on results of the eye, hand and foot screens, referral to appropriate medical and therapeutic interventions can prevent or minimize nerve damage and subsequent deformity.

Patient Education

Patients need to be educated on the autonomic, sensory and motor issues associated with peripheral nerve damage due to HD. They need to understand how to protect inflamed nerves, hydrate dry eyes and skin, protect insensate areas, and know who to contact at the first sign of problems. It is critical for patients to understand theconcept of "loss of protective sensation" (LOPS). Without protective sensation, the patient can sustain injuries, burns or ulcers from trauma or repetitive pressure withoutfeeling any pain. Patients with LOPS need education on methods to compensate for their lack of pain sensation, such as frequent inspection, protective equipment for the eyes and hands, and appropriate footwear.

Daily Self-Inspection

Patients with LOPS are taught to carefully inspect their eyes, hands and feet daily. They are to seek immediate treatment if they identify areas of redness, swelling, blisters, callus or wounds. Most patients with LOPS need ongoing education and reinforcement to develop and maintain effective self-inspection habits to prevent small issues from becoming major problems. While it is ideal for patients to inspect their own eyes and limbs, a family member or friend may need to assist if the patient is physically unable to perform daily inspection.

Management of Problems

Patients with enlarged/tender nerves, LOPS, weakness, deformities, thickened nails/callus and wounds require regular follow-up. A nerve affected by HD may becomeinflamed and swollen causing numbness, tingling, pain or weakness. As a result, a patient may be inclined to move the arm or leg to relieve the discomfort or to strengthen the weak limb. This additional movement may cause more damage to the nerve. Advising the patient to limit movement is encouraged, but an inflamed or painful nerve may require splinting to immobilize and protect the nerve from harm.

Upper Extremities: Patient can wear an elbow pad if needed, it will support the ulnar nerve at the elbow. A more rigid elbow splint made of thermoplastic material may be needed for more severe pain. A rigid elbow splint can also be used to immobilize the elbow for wound healing. A wrist splint will support the median nerve at the wrist. It should be worn at night while sleeping and can be worn during the day if needed to decrease the pain. The splints also protect the nerves during activity. Use of the arm should be decreased to rest the nerve.

Avoid repetitive motions

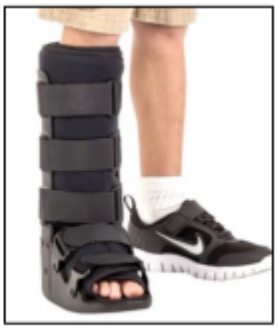
Elbow Pad (top) &
Wrist Splint bottom

Elbow Splint

Lower Extremities: A compression wrap, compression stockings, or a rigid walking boot may help to decrease swelling, immobilize the ankle and relieve discomfortin the leg.

Elastic Wraps

Compressive
Socks



Walking Boot

Routine care may be required to manage thickened nails and calluses to prevent wounds. An open wound becomes a risk for subsequent infection. Infections can go unnoticed dueto lack of sensation and lead to osteomyelitis, progressive shortening of the digits, and potentially amputation. Offloading pressure is the key to wound healing in patients with loss of sensation and deformities. Offloading is accomplished using adhesive felt, casts, splints and other devices. In addition to off-loading, wound management consistsof appropriate dressings, debridement of devitalized tissue and management of osteomyelitis. Patients with clawing or foot drop may benefit from specific exercises, splints and education to prevent contractures and progressive deformities. These patients may also be eligible for reconstructive surgery. To consult NHDP staff regardingnon-healing wounds, surgical candidates and difficult cases please call (800) 642-2477 or email HRSANHDPClinic@hrsa.gov).

Assistive Devices/ Footwear and Orthotics

The patient who lacks sensation can sustain injuries or wounds without noticing, even while performing simple daily activities. A combination of modified techniques and assistive/protective devices decrease the risk of injury and maximize independence in the performance of daily functional tasks.Some of these protective devices prevent injury by insulating from extreme heat and cold. Other devices prevent injury by reducing pressure and friction on the limb. Some commonly recommended adaptive and safety devices include the following:

Eyes:

Contoured eye mask – worn at night protects the eyes from dryness due toLagophthalmos.

Wrap-around sunglasses protect the eyes from dust, wind and exposure to UV light.

Broad brimmed hat protects the eyes fromexposure to UV light.

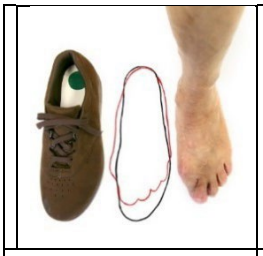
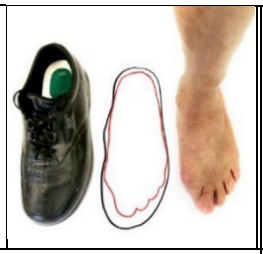
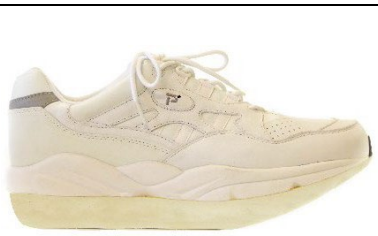
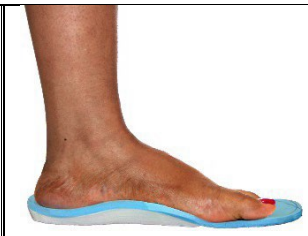
Hands: Long arm oven mitts protect the patient with loss of protective sensation while cooking or grilling outside. Insulated mugs prevent burns on the hand. Built up utensils and adapted devices make it easier for the patient with decreased strength or deformity to use their hands independently.

Long arm oven mitts

Insulated mugs

Tab grabber

Feet: Protective footwear cannot be overemphasized. Proper shoes and orthotics, worn as prescribed, can protect the feet from injury and ulceration. Improper footwear,or going barefoot, may lead to serious harm and cause ulceration. An expert, such as a Pedorthist or Podiatrist, must address the footwear and orthotic needs of a patient withLOPS and deformity.

			
Tight shoe	**Shoe that fits**	**Rigid Rocker Shoe**	**Custom insoles**

Patient understanding and compliance with prevention protocols is the most important aspect for prevention of injury and disability. For more information on POD, assistive devices, footwear, orthotics and vendors, see NHDP website: https://www.hrsa.gov/hansens-disease.

A patient with decreased corneal sensation in the eyes or LOPS in the hands and feet must be monitored indefinitely - even after being released from medical treatment.

SURGICAL INTERVENTION

For appropriate candidates, surgery may be an option to expedite wound healing, minimize deformity and maximize function. Depending on the patient's need and condition, the following surgical procedures may be considered:

Hands and Feet

Debridement – Surgical removal of non-viable tissue including infected bone to promote wound healing.
Skin Graft/Flap – Once a wound is devoid of all non-viable tissue, a skin graft or flapmay expedite wound healing.
Tendon Transfer – A tendon transfer procedure involves moving or transferring thetendon insertion of a healthy muscle to the insertion site of a weak or paralyzed muscle(s) in order to restore balance and function to the limb. This procedure is used to correct mobile claw hand deformity and to correct a foot drop.
Ulnar Nerve Transposition – This procedure is used to decrease pain and prevent entrapment of the ulnar nerve in the cubital tunnel.
Tendon Release – A tendon release procedure, such as an Achilles tendon lengthening, or toe flexor release may help reduce high-pressure areas that translateonto the foot.
Arthrodesis – An arthrodesis involves fusing a joint to improve the position of the digit. This procedure is used for longstanding paralysis where a contracteddigit has resulted in joint subluxation.
Amputation - An amputation is a last resort procedure to improve quality of life, or when function will be increased byprosthetic usage.
Osteotomy – This procedure involves removal of a rigid and prominent bony deformity in order to decrease high-pressure areas.

Eyes

Patients on high dose steroids should be monitored for elevated intraocular pressure to prevent glaucoma. Patients who develop lagophthalmus will also need a consult with ophthalmology. Potential surgical procedures include tarsorrhaphy, laser iridectomy, trabeculoplasty and cataract.

CONTACT EVALUATION

Contact:

In the U.S., a Hansen's disease "contact" is defined as a person living in the same household with a new patient in the three-year period prior to the beginning of treatment. Examination of contacts of diagnosed patients is the simplest and only practical form of active case finding in low incidence areas such as the United States. This examination can be performed by a medical provider.

The patient always has a right to privacy and may refuse to notify a contact that they have been diagnosed with HD. In that case, treat the patient as anyone exercising the right to privacy.

If a person becomes aware that they are a contact, they may wish to be evaluated.

Contact Examinations:

Examine the entire skin surface.

Nerve function assessment of the peripheral nerves, focusing primarily on the eyes,hands, and feet (See Forms at https://www.hrsa.gov/hansens-disease).

Contact Follow-Up:

Contacts with a negative initial exam do not need follow-up if the patient has beeneducated about the disease and what symptoms should be reported to the health care provider.

Chemoprophylaxis:

Chemoprophylaxis should be considered on a case-by-case basis. Contact NHDP for consultation and a recommendation regarding prophylaxis of individual contacts. There are no known intermediate hosts and *M. leprae* does not survive for long periods outside the body. There is no vaccine available. At present, there is no practical means of primary prevention, (i.e. the detection and protection of persons at risk). Hansen's disease control is based on secondaryprevention; that is, the early detection and regular treatment of all detected cases existing in an area.

The NHDP does not utilize pre- or post-exposure prophylaxis for healthcare workers.

Additional information about current chemoprophylaxis guidelines and criteria by the World Health Organization can be found on the WHO website.

AMBULATORY CARE PROGRAM

Individuals living in the United States and its territories (Puerto Rico, US Virgin Islands, Guam, Northern Mariana Islands, and American Samoa) may receive medical care for the diagnosis and treatment of HD related conditions at one of the federally supported outpatient clinics throughout the USA. Contact the NHDP at 1-800-642-2477, weekdays- 8a.m. to 4:30 p.m. CST, or email to HRSANHDPCLINIC@HRSA.GOV for referral to one of the ambulatory care clinics.

Services may include:

- Confirmation of diagnosis through histopathologic examination of skin biopsies
- PCR testing
- Medical care for Hansen's disease and its complications
- HD-related medications at no cost to the patient
- Consultation on patients with eye, hand and foot problems for specialized treatment
- Professional and patient education materials

Locations:

Additional information for each clinic is located on the NHDP Website under the heading "Ambulatory Care Clinics":

https://www.hrsa.gov/hansens-disease/ambulatory-clinics.html

The Hawaii Department of Health operates a clinic independent of the National Hansen's Disease Programs.

PRIVATE PHYSICIANS

HD-related medications can be provided to patients living in an area not served by an Ambulatory CareHD clinic through a private physician.

A physician can request HD-related medications from the NHDP at no charge to the patient. Consultation and biopsy processing services are also provided by the NHDP free of charge atthe physician's request.

For treatment options, patients in the United States and its territories can contact the NHDP at 1-800-642-2477,weekdays 8 a.m. to 4:30 p.m. CST. In Hawaii, HD patients can call 1-808-733-9831.

REPORTING REQUIREMENTS

Surveillance Form:

The NHDP maintains a National HD Registry for all patients diagnosed with Hansen's diseasein the U.S. ***A completed HD Surveillance Form is required on all patients diagnosed in the US***. The Form can be found on the front page of the NHDP website https://www.hrsa.gov/hansens-disease

Completion and receipt of the Surveillance Form is required before medications are shipped. Fax 225-756-3706

Forms:

The following forms are highly recommended to manage and monitor patient care while on antibiotic treatment and after the completion of treatment for a minimum of three years. The forms include tools for screening patients for disability, ordering clinical laboratory services from NHDP, monitoring

for disability, and behavioral health screening. Early detection of ENL and disability status can help with better patient outcomes to include decreased disability.

Behavioral Health Screeners help providers detect issues early so that interventions and referrals can be placed sooner to help the patient achieve better outcomes while being treated and managed for HD.

The following forms can be location at the NHDP website https://www.hrsa.gov/hansens-disease

- Skin Biopsies (Consent, Instructions, Form)
- Protocol for Submitting Specimens for Histological Evaluation to the NHDP
- Skin Smears (Instructions)
- Surveillance Form
- Annual Follow-Up Form
- Eye Screen Form
- Hand Screen Form
- Foot Screen Form
- Healthy Eyes, Hands, and Feet for Lifetime
- Nail Care
- Callus and Skin Care
- Wound Management
- Basic Wound Care
- Off-loading – Adhesive Felt Relief
- Off-loading – Toe Pillow Fabrication
- Behavioral Health Screeners

RESOURCES

NHDP Resources for HD include:

- Consultation on the diagnosis, treatment and management of Hansen's disease and HD-related immunological reactions
- Histopathologic examination of skin biopsies, evaluation of Fite stained skin smearsand molecular testing (Polymerase Chain Reaction - PCR) at no cost to the patient
- Consultation regarding treatment for HD related complications including neuropathic limb care, wound care, prevention of disability, and orthopedic procedures

- Behavioral health consultation, screening and education about HD-related mental health issues and stigma
- Medications for treatment of HD at no cost to the patient
- Educational seminars for Physicians, Nurses, Occupational Therapists, Physical Therapists, Orthotists, Podiatrists, and Behavioral Health Providers
- Online and in person courses for diagnosis and treatment of HD and Lower Extremity Amputation Prevention. Additional HD seminar materials can be located on our website or on YouTube.
    - YouTube HRSA NHDP When to Suspect Leprosy
    - YouTube HRSA NHDP Slit Skin Smear
- NHDP Website- https://www.hrsa.gov/hansens-disease

Information regarding these services is available from:
National Hansen's Disease Program
9181 Interline Avenue
Baton Rouge, LA, 70809
Phone: 800-642-2477 Fax: 225-756-3706

Other Resources

- Global Program for Zero Leprosy https://zeroleprosy.org/
- The Leprosy Mission International https://www.leprosymission.org/
- Leprosy Mailing List Blog http://leprosymailinglist.blogspot.com
- History of Leprosy http://www.leprosyhistory.org
- The National Hansen's Disease Museum https://www.hrsa.gov/hansens-disease/museum/index.html
- The International Textbook of Leprosy http://www.internationaltextbookofleprosy.org/
- Up-to-Date http://www.uptodate.com/