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section 8 Infectious diseases 1154 little evidence to support these regimens and expert consultation should be sought. For M. chelonae, tobramycin or imipenem can be combined with a macrolide, with macrolide-fluoroquinolone combinations for subsequent oral therapy. Macrolides may not be effective against M. fortuitum owing to natural resistance and a multidrug regimen that combines a quinolone with trimethoprim- sulfamethoxazole, doxycycline, an aminoglycoside, or imipenem can be used. Treatment duration in pulmonary disease by rapid growers is not well studied; for M. abscessus it equals that of MAC, for other species it may be shorter based on clinical and bacterio- logical response. Cure rates of pulmonary disease by environmental mycobacteria are limited, in the 50–70% range; M. kansasii disease has more fa- vourable outcome. Adjunctive surgical resection of the affected areas of the lung improves outcomes in selected cases. To achieve success in the treatment of environmental mycobac- terial disease, optimal treatment of the underlying and predisposing conditions is vital. FURTHER READING Bryant JM, et al. (2016). Emergence and spread of a human- transmissible multidrug-resistant nontuberculous mycobacterium. Science, 354, 751–7. Falkinham JO III (2009). Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. J Appl Microbiol, 107, 356–67. Floto RA, et al. (2016). US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the man- agement of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax, 71 (Suppl 1), 1–22. Griffith DE, et al. (2007). An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial dis- eases. Am J Respir Crit Care Med, 175, 367–416. Lindeboom JA, et al. (2007). Surgical excision versus antibiotic treat- ment for nontuberculous mycobacterial cervicofacial lymph- adenitis in children: a multicenter, randomized, controlled trial. Clin Infect Dis, 44, 1057–64. Research Committee of the British Thoracic Society (2008). Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of Mycobacterium vaccae immunotherapy. Thorax, 63, 627–34. Wolinsky E (1979). Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis, 119, 107–59. 8.6.28 Leprosy (Hansen’s disease) Diana N.J. Lockwood ESSENTIALS Leprosy is a chronic granulomatous disease caused by Mycobacterium leprae, an acid-fast intracellular organism not yet cultivated in vitro. It is an

important public health problem worldwide, with an estimated 4 million people disabled by the disease. Transmission of M. leprae is only partially understood, but untreated lepromatous patients discharge abundant organisms from their nasal mucosa into the environment. Clinical features These are determined by the degree of cell-mediated immunity towards M. leprae, with tuberculoid (paucibacillary) and leproma- tous leprosy (multibacillary) being the two poles of a spectrum: (1) tuberculoid—well-expressed cell-mediated immunity effectively controls bacillary multiplication with the formation of organized epithelioid-cell granulomas; (2) lepromatous—there is cellular anergy towards M. leprae with abundant bacillary multiplication. Between these two poles is a continuum, varying from the patient with mod- erate cell-mediated immunity (borderline tuberculoid), through borderline, to the patient with little cellular response, borderline lepromatous. Presenting symptoms—most commonly (1) anaesthesia—ranging from a small area of numbness on the skin due to involvement of a dermal nerve, to peripheral neuropathy with affected nerves tender and thickened; (2) skin lesions—most commonly macules
or plaques; tuberculoid patients have few, hypopigmented lesions that are anaesthetic; lepromatous patients have numerous, some- times confluent lesions. Other manifestations—these include (1) type 1 (reversal reactions)— occur in borderline patients; characterized by acute neuritis and/or acutely inflamed skin lesions; often occur in the first 2 months after starting treatment; (2) type 2 (erythema nodosum leprosum reac- tions)—occur in up to 50% of patients with lepromatous leprosy; (3) neuritis—silent neuropathy is an important form of nerve damage, causing lifelong morbidity; (4) eye disease—blindness occurs in at least 2.5% of patients. Diagnosis This is made by recognition of typical skin lesions or thickened per- ipheral nerves, supported by the finding of acid-fast bacilli on slit skin smears that should be taken from at least four sites (earlobes, and edges of active lesions). Treatment There are six main principles of treatment: (1) stop the infection with chemotherapy—first-line antileprosy drugs are rifampicin, clofazimine, and dapsone, given in combination and duration as determined by whether disease is paucibacillary or multibacillary; these are highly effective in killing bacilli but may not halt nerve damage; (2) treat new nerve damage—a 6-month course of ster- oids should be given to those with nerve damage for less than 6 months; (3) treat reactions—steroids are likely to be required; (4) educate the patient about leprosy; (5) prevent disability; and (6) support the patient socially and psychologically—patients with leprosy the world over are frequently stigmatized; words such as ‘leper’ should be avoided; the disease can be referred to as ‘Hansen’s disease’. Prevention Vaccination with Bacille Calmette–Guérin (BCG) can provide some protection against leprosy (20–80% in different trials).

8.6.28 Leprosy (Hansen’s disease) 1155 Aetiology Leprosy is caused by Mycobacterium leprae, an acid-fast intracel- lular organism not yet cultivated in vitro. It was first identified in the nodules of patients with lepromatous leprosy by Hansen in 1873. M. leprae preferentially parasitizes skin macrophages and periph- eral nerve Schwann cells. A second agent of leprosy, M. lepromatosis, which diverged form M. leprae 10 million years ago has also been recognized as causing leprosy in about 40 patients and the main focus of origin is Mexico. The importance of this organism will be determined over the next few years. In vivo cultivation of M. leprae M. leprae can be grown in the mouse footpad, but growth is slow, taking over 6 months to produce significant yields. The nine-banded armadillo is susceptible to M. leprae infection and develops lepromatous disease. The armadillo and mouse models of M. lep- rae infection have been useful for producing M. leprae for bio- logical studies and studying drug sensitivity patterns, respectively. Biological characteristics M. leprae is a stable hardy organism that withstands drying for up to 5 months. It has a doubling

time of 12 days (compared with 20 min for Escherichia coli). The optimum growth temperature is 27 to 30° C, consistent with the clinical observation of maximal M. leprae growth at cool superficial sites (skin, nasal mucosa, and peripheral nerves). M. leprae isolates from different parts of the world have similar biological characteristics. M. leprae possesses a complex cell wall comprising lipids and carbohydrates. It synthesizes a species- specific phenolic glycolipid and lipoarabinomannan. Antibody and T-cell screening have identified numerous protein antigens and pep- tides that are important immune targets. M. leprae genome M. leprae has a 3.27-Mb genome that displays extreme reductive evolution. Less than one-half of the genome contains functional genes and many pseudogenes are present. One hundred and sixty- five genes are unique to M. leprae and functions can be attributed to 29 of them. These unique proteins are being identified and analysed to aid in development of new diagnostic tests. Comparison of bio- synthetic pathways with Mycobacterium tuberculosis is giving new insights into M. leprae metabolism. For lipolysis M. leprae has only two genes (M. tuberculosis has 22); M. leprae has also lost many genes for carbon catabolism and many carbon sources (e.g. acetate and galactose) are unavailable to it. This gene loss leaves M. leprae unable to respond to different environments and underlies the impossibility of growing the organism in vitro. Using comparative genomics and analysis of single nucleotide polymorphisms it has been shown that all extant cases of leprosy can be attributed to a single clone which then disseminated worldwide. Leprosy probably originated in India or eastern Africa and spread with successive human migrations. Epidemiology Leprosy continues to be an important public health problem worldwide. In 2014, 213 889 new cases were detected and registered. The highest numbers of cases were in India, Brazil, Indonesia, Ethiopia, and Bangladesh. India accounts for 58% of the global dis- ease burden. From 1990, the World Health Organization (WHO) led a leprosy elimination campaign and this defined elimination as less than 1 case per 10 000 population. Prevalence figures are highly influenced by operational activities such as reducing the length of treatment. The global focus is now on detecting new cases and pro- viding sustainable care for leprosy patients. An estimated 4 million people are disabled by leprosy. Leprosy has not always been a trop- ical disease; it was widespread in medieval Europe and was endemic in Norway until the early 20th century. In North America, small foci of infection still exist in Texas and Louisiana. Nearly all new patients now seen in Europe and North America have acquired their infec- tion abroad. Risk factors Leprosy is a chronic disease with a long incubation period. An average incubation time of 2 to 5 years has been calculated for tu- berculoid cases and 8 to 12 years for lepromatous cases. American servicemen who developed leprosy after serving in the tropics pre- sented up to 20 years after their presumed exposure. Most leprosy patients do not have known contact with a leprosy patient. Age, sex, and household contact are important determinants of leprosy risk; incidence reaches a peak at 10 to 14 years; the excess of male cases is attributed to women’s reluctance to present to health workers with skin lesions. Poor nutritional status is cited as predisposing to leprosy, but no good evidence substantiates this. Improved socioeconomic conditions, extended schooling, and good housing conditions reduce the risk of leprosy. Subclinical infection with M. leprae is probably common but the development of established disease is rare. Little work has been done on the early events in infec- tion with M. leprae because there is no simple test that can establish whether an individual has encountered M. leprae and mounted a protective immune response. HIV and leprosy It was predicted that HIV infection would produce anergic, leproma- tous leprosy, However HIV/leprosy coinfected patients have disease types across the leprosy spectrum with typical leprosy skin lesions and nerve involvement. Their skin lesions have typical leprosy hist- ology with granuloma formation even in the presence of low cir- culating CD4 counts. Patients coinfected with HIV and leprosy are at higher

risk of developing leprosy reactions and nerve damage. Leprosy might also present as an immune reconstitution syndrome in patients who have recently started on highly active antiretroviral therapy and have rising CD4 counts. These patients have borderline leprosy which is very immunologically active with inflamed skin le- sions and reactions. Transmission The transmission of M. leprae is only partially understood. Untreated lepromatous patients discharge abundant organisms from their nasal mucosa into the environment. Studies in Indonesia and Ethiopia using polymerase chain reaction primers to detect M. leprae DNA in nasal swabs have shown that up to 5% of the population in leprosy endemic areas carry M. leprae DNA in their

section 8 Infectious diseases 1156 noses. The organism is then inhaled, multiplies on the inferior tur- binates, and has a brief bacteraemic phase before binding to and entering Schwann cells and macrophages. The combination of an environmentally well-adapted organism, high carriage rates, and a long incubation period means that, even with effective antibiotics, transmission will continue for a long time. Pathogenesis Leprosy is a bacterial infection in which the clinical features are determined by the host's immune response (Table 8.6.28.1). Immune response to M. leprae and the leprosy spectrum The Ridley–Jopling classification (Fig. 8.6.28.1) places patients on a spectrum of disease according to their clinical features, bacterial load, and histological and immunological responses. The two poles of the spectrum are tuberculoid (TT; paucibacillary) and leproma- tous leprosy (LL; multibacillary). At the tuberculoid pole, well- expressed cell-mediated immunity effectively controls bacillary multiplication with the formation of organized epithelioid-cell granulomas; at the lepromatous pole there is cellular anergy to- wards M. leprae with abundant bacillary multiplication. Between these two poles is a continuum, varying from the patient with moderate cell-mediated immunity (borderline tuberculoid, BT) through borderline (BB) to the patient with little cellular response, borderline lepromatous (BL). The polar groups (TT, LL) are stable, but within the central groups (BT, BB, BL) the disease tends to downgrade to the lepromatous pole in the absence of treatment, and upgrading towards the tuberculoid pole can occur during or after treatment. Both T cells and macrophages play important roles in the pro- cessing, recognition, and response to M. leprae antigens. In tuber- culoid leprosy, in vitro tests of T-cell function, such as lymphocyte transformation tests, show a strong response to M. leprae pro- tein antigens with the production of Th1-type cytokines such as interferon-γ and interleukin 2 (IL-2). Skin tests with lepromin, a heat-killed M. leprae preparation, are strongly positive. Staining of skin biopsies from tuberculoid lesions with T-cell markers shows highly organized granulomas composed predominantly of CD4 cells and macrophages with a peripheral mantle of CD8 cells. This strong cell-mediated immune response clears bacilli but with concomitant local tissue destruction, especially in nerves. Patients with lepromatous leprosy have no cell-mediated im- munity to M. leprae with a failure of the T-cell and macrophage response. Tests for lepromin are negative. This anergy is spe- cific for M. leprae. Patients with lepromatous disease respond to other mycobacteria such as M. tuberculosis, both in vitro and in skin tests. Identification of cell types in lepromatous granulomas shows a disorganized mixture of macrophages and T cells, mainly CD8 cells. The T-cell failure may be due to clonal anergy or active suppression. Defects in cytokine production have been demon- strated; intralesional injections of recombinant IL-2 reconstitute the local immune response with elimination of M. leprae from macrophages. There is low production of Th2-type cytokines. Macrophage defects described in lepromatous disease include defective antigen presentation and recognition, defective IL- 1 production, a failure of macrophages to kill M. leprae, and a macrophage suppression of the T-cell response. Patients with lep- romatous leprosy produce a range of autoantibodies that are both organ specific (against thyroid, nerve,

testis, and gastric mucosa) and nonspecific, such as rheumatoid factors, anti-DNA, cryo- globulins, and cardiolipin. Table 8.6.28.1 Major clinical features of the disease spectrum in leprosy Clinical features Classification Tuberculoid (TT) Borderline tuberculoid (BT) Borderline (BB) Borderline lepromatous (BL) Lepromatous (LL) Paucibacillary Multibacillary Skin Infiltrated lesions Defined plaques, healing centres Irregular plaques with partially raised edges Polymorphic, ‘punched-out centres’ Papules, nodules Diffuse thickening Macular lesions Single, small Several, any size, ‘geographical’ Multiple, all sizes,
bizarre Innumerable, small Innumerable, confluent Nerve Peripheral nerve Solitary enlarged nerves Several nerves, asymmetrical Many nerves, asymmetrical pattern Late neural thickening, asymmetrical, anaesthesia, and paresis Slow symmetrical loss, glove and stocking anaesthesia Microbiology Bacterial index 0–1 0–2 2–3 1–4 4–6 Histology Lymphocytes + ++ ± ++ ± Macrophages – – ± – – Epithelioid cells ++ ± – – – Antibody, anti-M. leprae –/+ –/++ + ++ ++ +, present, ++, present strongly, –, absent.

 Bacterial load In lepromatous leprosy, bacilli spread haematogenously to cool superficial sites including eyes, upper respiratory mucosa, testes, small muscles, and bones of the hands, feet, and face as well as to peripheral nerves and skin. The heavy bacterial load causes struc- tural damage at all these sites. In tuberculoid leprosy, bacilli are not readily found. Nerve damage Neural inflammation is pathognomonic of leprosy. Nerve damage occurs in small nerve fibres, both sensory and autonomic, in the skin, and in peripheral nerve trunks. Nerve damage occurs before diagnosis, during treatment, and after treatment. In lepromatous in- fection, almost all the cutaneous nerves and peripheral nerve trunks are involved. Bacilli are found in Schwann, perineural, and endothe- lial cells. Extensive demyelination occurs and later wallerian degen- eration. Despite large numbers of organisms in the nerve there is only a small inflammatory response, but ultimately the nerve becomes fibrotic and is hyalinized. At the tuberculoid end of the spectrum nerve damage is secondary to a granulomatous response to M. lep- rae antigens. Perineural inflammation and epithelioid granulomas destroy the Schwann cells and axons. In borderline leprosy the com- bination of M. leprae antigens and a cell-mediated immune response results in small granulomas abutting strands of normal-looking but heavily bacillated Schwann cells giving rise to the widespread nerve damage in borderline leprosy. The persistence of M. leprae antigens in Schwann cells means that immune-mediated nerve damage can occur after successful antibacterial treatment. Leprosy reactions Leprosy reactions are episodes of inflammation that occur across the Ridley–Jopling spectrum. Type 1 (reversal reactions) occur in bor- derline patients (BT, BB, BL) and are delayed hypersensitivity reac- tions caused by increased recognition of M. leprae antigens in skin and nerve sites. They are characterized by an increase in lympho- cytes (CD4 and IL-2-producing cells) within lesions, severe oedema with disruption of the granuloma, and giant cell formation. There is local production of Th1-type cytokines such as interferon-γ and tumour necrosis factor-α. Type 2 reactions, erythema nodosum leprosum (ENL), are partly due to immune complex deposition and occur in patients with borderline lepromatous and lepromatous leprosy who pro- duce antibodies and have a large antigen load. There is vasculitis with lesional immunoglobulin deposition, complement activation, and polymorphs and circulating immune complexes. There is also enhanced T-cell activity with increased CD8 cells, increased circu- lating IL-2 receptors, and high levels of circulating tumour necrosis factor-α. After reaction, lepromatous patients revert to a state of immunological unresponsiveness. Clinical features of leprosy Patients commonly present with skin lesions, weakness, or numb- ness due to a peripheral nerve lesion, or a burn or ulcer on an anaes- thetic

hand or foot. Borderline patients may present in reaction with nerve pain, sudden palsy, multiple new skin lesions, pain in the eye, or a systemic febrile illness. The cardinal signs are: • typical skin lesions, anaesthetic at the tuberculoid end of the spectrum • thickened peripheral nerves • acid-fast bacilli on skin smears or biopsy Early lesions The most common early lesion is an area of numbness on the skin or a visible skin lesion. The classic early skin lesion is indeterminate leprosy, which is commonly found on the face, extensor surface of the limbs, buttocks, or trunk. Indeterminate lesions consist of one or more slightly hypopigmented or erythematous macules, a few centimetres in diameter, with poorly defined margins. Hair growth and nerve function are unimpaired. A biopsy may show the perineurovascular infiltrate and only scanty acid-fast bacilli. The in- determinate phase may last for months or years before resolving or developing into one of the determinate types of leprosy. Skin The most common skin lesions are macules or plaques; papules and nodules are more rare. Lesions can be found anywhere although rarely in the axillae, perineum, or hairy scalp. Skin lesions should be assessed for inflammation, colour, and sensation. Tuberculoid patients have few granulomatous hypopigmented lesions while lep- romatous patients have numerous, sometimes confluent lesions. The few tuberculoid lesions are usually asymmetrical; more numerous lesions are likely to be distributed symmetrically. Anaesthesia Anaesthesia may occur in skin lesions when dermal nerves are in- volved or in the distribution of a large peripheral nerve. In skin lesions the small dermal sensory and autonomic nerve fibres supplying dermal and subcutaneous structures are damaged causing local sensory loss and loss of sweating within that area. Peripheral neuropathy Peripheral nerve trunks are vulnerable at sites where they are super- ficial or are in fibro-osseous tunnels. At these points a small in- crease in nerve diameter raises intraneural pressure, causing neural Cell mediated Immunity TT BT BB BL LL Bacterial load 0 3 6 Type 1 reactions ENL reactions Fig. 8.6.28.1 Ridley–Jopling spectrum of bacterial load, cell-mediated immunity, and reactions.

section 8 Infectious diseases 1158 compression and ischaemia. Damage to peripheral nerve trunks produces characteristic signs with dermatomal sensory loss and dysfunction of muscles supplied by that peripheral nerve. The pre- dilection sites for peripheral nerve involvement are ulnar nerve (at the elbow) (Fig. 8.6.28.2), median nerve (at the wrist), radial nerve, radial cutaneous nerve (at the wrist), common peroneal nerve (at the knee), posterior tibial and sural nerves at the ankle, facial nerve as it crosses the zygomatic arch, and great auricular nerve in the pos- terior triangle of the neck (Fig. 8.6.28.3). All these nerves should be examined for enlargement and tenderness. Peripheral nerve func- tion should be assessed by testing the motor function of the small muscles of the hands and feet using the Medical Research Council (MRC) grading scale. Sensory function is best assessed using graded nylon monofilaments (Semmes–Weinstein) as in diabetic screening. Patients should be asked about symptoms of neuropathy. Tuberculoid leprosy (TT) Infection is localized and asymmetrical. A typical tuberculoid skin lesion is a macule or plaque, single, erythematous, or purple, with raised and clear-cut edges sloping towards a flattened hypopigmented centre. The surface is anaesthetized, dry, and hairless. Sensory im- pairment can be difficult to demonstrate on the face where there are abundant nerve endings. If peripheral nerve trunk involvement is present, only one nerve trunk is enlarged. No M. leprae are found in skin smears. True tuberculoid leprosy has a good prognosis, many infections resolve without treatment, and peripheral nerve trunk damage is limited. Borderline tuberculoid leprosy (BT) The skin lesions are similar to tuberculoid leprosy and there may be few or many lesions (Figs. 8.6.28.4, 8.6.28.5). The margins are less well defined and there may be satellite lesions. Damage to periph- eral nerves is widespread and severe, usually with several thickened nerve trunks. It is important to recognize

borderline tuberculoid lep- rosy because these patients are at risk of reversal reactions leading to rapid deterioration in nerve function with consequent deformities. Borderline leprosy (BB) Borderline disease is the most unstable part of the spectrum and patients usually downgrade towards lepromatous leprosy if they are not treated or upgrade towards tuberculoid leprosy as part of a reversal reaction. There are numerous skin lesions which may be macules, papules, or plaques, and they vary in size, shape, and dis- tribution. The edges of the lesions may have streaming, irregular borders. Annular lesions with a broad irregular edge and a sharply defined punched-out centre are characteristic of borderline disease (Fig. 8.6.28.6). Nerve damage is variable. Borderline lepromatous leprosy (BL) This is characterized by widespread variable asymmetrical skin le- sions. There may be erythematous or hyperpigmented papules, succulent nodules or plaques, and sensation in the lesions may be Fig. 8.6.28.2 The effects of ulnar and median nerve paralysis
with wasting of the small muscles of the hand and evidence of neuropathic damage. Copyright D. A. Warrell. Fig. 8.6.28.3 Thickening of greater auricular nerve. Copyright D. A. Warrell. Fig. 8.6.28.4 BT leprosy. This Ethiopian woman was several hypopigmented patches. Testing for anaesthesia will confirm the diagnosis of BT leprosy.

 normal (Fig. 8.6.28.7). Peripheral nerve involvement is widespread. While patients with borderline lepromatous leprosy do not have the extreme consequences of bacillary multiplication that are seen in lepromatous disease, they might experience either or both reversal and ENL reactions. Lepromatous leprosy (LL) The patient with untreated polar lepromatous leprosy might be carrying 1011 leprosy bacilli. The onset of disease is frequently in- sidious, the earliest lesions being ill-defined, shiny, hypopigmented, or erythematous macules. Gradually the skin becomes infiltrated and thickened and nodules develop (Fig. 8.6.28.8); facial skin thickening causes the characteristic leonine facies (Fig. 8.6.28.9). Hair is lost, especially the lateral third of the eyebrows (madarosis). Dermal nerves are destroyed leading to a progressive glove and stocking anaesthesia. Position sense is preserved. Sweating is lost, which is uncomfortable in the tropics as compensatory sweating occurs in the remaining intact areas. Damage to per- ipheral nerves is symmetrical and occurs late in the disease. Infiltration of the corneal nerves causes anaesthesia of the cornea, which predisposes to injury, secondary infection, and blindness (Fig. 8.6.28.10). Nasal symptoms can often be elicited early in the disease. Septal perforation can occur. There might be papules on the lips and nodules on the palate, uvula, tongue, and gums (Fig. 8.6.28.11). Bone involvement is common, with absorption of the terminal phalanges and pencilling of the heads and shafts of the metatarsals. Fig. 8.6.28.5 Active tuberculoid lesions showing the sharp outer edge, thin raised erythematous dry rim, and the broad hypopigmented dry centre. The ‘satellite’ lesion at the lower outer edge indicates that this is borderline tuberculoid leprosy. Biopsies and smears should be taken from the raised active rim. Copyright D. A. Warrell. Fig. 8.6.28.6 Multiple, asymmetrical erythematous lesions in BB leprosy. Sensation was intact inside the lesions. Fig. 8.6.28.7 BL leprosy with multiple erythematous lesions. No anaesthesia was present. Fig. 8.6.28.8 Advanced nodular lepromatous leprosy. This Indian patient presented with ulcerating nodules all over his body.

 Testicular atrophy results from diffuse infiltration compounded by acute orchitis that can occur during ENL reactions. The conse- quent loss of testosterone leads to azoospermia and gynaecomastia (Fig. 8.6.28.11). The extremities become oedematous. The skin of the legs becomes ichthyotic and ulcerates easily. Other forms of leprosy There are several

variant forms of leprosy. Pure neural leprosy, when patients have no skin lesions, has been reported from India and Brazil where it is the presenting form for up to 10% of patients. There is asymmetrical involvement of peripheral nerve trunks and no visible skin lesions. On nerve biopsy all types of leprosy have been found. Histoid lesions are distinctive nodules occurring in lepromatous patients who have relapsed due to dapsone resistance or noncompliance with chemotherapy. Lucio's leprosy is a form of lepromatous leprosy found only in Latin Americans; it is characterized by a uniform diffuse shiny skin infiltration. Eye disease in leprosy Blindness due to leprosy, which occurs in at least 2.5% of patients, is a devastating complication for a patient with anaesthesia of the hands and feet. Eye damage results from both nerve damage and bacillary invasion. Lagophthalmos results from paresis of the orbicularis oculi due to involvement of the zygomatic and temporal branches of the facial (VIIth) nerve. These superficial branches are frequently involved in borderline tuberculoid cases, particularly if there are facial skin lesions. In lepromatous dis- ease, lagophthalmos occurs later and is usually bilateral. Damage to the ophthalmic branch of the trigeminal (Vth) nerve causes anaesthesia of the cornea and conjunctiva resulting in drying of the cornea and making the cornea susceptible to trauma and ulceration (Fig. 8.6.28.12). Lepromatous infiltration in cor- neal nerves produces punctate keratitis and corneal lepromas. Invasion of the iris and ciliary body makes them extremely sus- ceptible to reactions. Leprosy reactions Type 1 (reversal reactions) These are characterized by acute neuritis and/or acutely inflamed skin lesions. Nerves become tender with new loss of sensation or motor weakness. Existing skin lesions become erythema- tous or oedematous (Figs. 8.6.28.13 and 8.6.28.14); new lesions Fig. 8.6.28.9 Lepromatous leprosy. Copyright D. A. Warrell. Fig. 8.6.28.10 Active, untreated lepromatous leprosy, showing generalized infiltration of the skin, swelling of fingers and lips, and thinning of eyebrows and eyelashes. The residual annular lesions visible in both pectoral regions indicate that this patient has 'downgraded' from borderline. Fig. 8.6.28.11 Complications of lepromatous leprosy. Gynaecomastia is visible in this man, secondary to testicular involvement in lepromatous leprosy. Multiple nodules are present, many dark brown, due to clofazimine pigmentation. He also has new erythematous lesions of ENL.

 might appear (Fig. 8.6.28.15). Occasionally oedema of the hands, face, or feet is the presenting symptom, but constitutional symp- toms are unusual. Type 1 reactions occur in borderline patients; 35% of borderline lepromatous patients will experience a type 1 reaction. Patients often present with a skin lesion in reaction since a previously quiescent lesion has become active and visible. The peak time for reactions in the first 2 months after starting treatment and in the puerperium. Late reactions can occur years after finishing multidrug treatment. Some patient experience re- peated reactions (Fig. 8.6.28.15). Type 2 (ENL reactions) These occur in lepromatous and borderline lepromatous pa- tients. Up to 50% of lepromatous patients will experience ENL reactions and 5–10% of borderline lepromatous patients. Attacks are acute and may recur over several years. ENL mani- fests most commonly as painful red nodules on the face (Fig. 8.6.28.16) and extensor surfaces of limbs (Fig. 8.6.28.17). The lesions can be superficial or deep, with suppuration or brawny induration when chronic. Acute lesions crop and desquamate, fading over several days. ENL is a systemic disorder producing fever and malaise and may be accompanied by uveitis, dactylitis (Fig. 8.6.28.18), arthritis, neuritis, lymphadenitis, and orchitis. Recent studies have established the importance of pain as a marker of severity. ENL is often not recognized as a complication of leprosy outside endemic areas. Fig. 8.6.28.12 Corneal damage to eye secondary to lagophthalmos caused by involvement of the zygomatic branch of the facial nerve. Fig. 8.6.28.14 Reversal-reaction plaque on the left cheek and ear. The edge of this

borderline tuberculoid lesion has become very sharply defined, more raised, and erythematous, dry, and scaly. Treatment with corticosteroids is imperative as the patient is at grave risk of rapidly developing lagophthalmos due to associated involvement of branches of the facial nerve.
Fig. 8.6.28.15 Type 1 (reversal) reaction: this BL patient
developed new, sharp-edged, well-defined, erythematous
plaques with desquamating surfaces about 6 months after starting chemotherapy. Fig. 8.6.28.13 Severe reversal (type 1) reaction. This Indian
woman has erythematous, oedematous, and desquamating reactional lesions.

section 8 Infectious diseases 1162 Neuritis Silent neuropathy is an important form of nerve damage and presents as a functional neural deficit without a manifest acute or subacute neuritis (Figs. 8.6.28.2, 8.6.28.3, 8.6.28.19 and 8.6.28.20). An Indian study following a cohort of 2608 patients found that 75% of those developing deformity had no history of reactions. In Ethiopian and Bangladeshi cohort studies, silent neuritis accounted for most neuritis. This emphasizes the import- ance of regular nerve function testing so that new deficits can be detected. Fig. 8.6.28.16 Erythema nodosum leprosum (ENL) on the forehead of a patient with early lepromatous leprosy. The papules (and nodules) are firm and tender, with rather indefinite edges. In dark-skinned patients the ENL lesions are often easier to feel than to see, especially over the extensor surfaces of the arms and thighs. Copyright D. A. Warrell. Fig. 8.6.28.17 Erythema nodosum leprosum (ENL) of the shins. Copyright D. A. Warrell. Fig. 8.6.28.18 Dactylitisas part of an ENL reaction. Copyright D. A. Warrell. Fig. 8.6.28.19 Peripheral nerve thickening in leprosy. This young man had marked thickening of his great auricular nerve. Fig. 8.6.28.20 This foot shows thick, dry cracked skin together with neuropathic damage in an anaesthetic foot. The toes are clawed, the foot arch has collapsed and there is evidence of a Charcot ankle joint.

8.6.28 Leprosy (Hansen’s disease) 1163 Diagnosis The diagnosis is made on the clinical findings of one or more of the cardinal signs of leprosy and supported by the finding of acid-fast bacilli on slit skin smears. The whole body should be inspected in a good light otherwise lesions may be missed, particularly on the but- tocks. Skin lesions should be tested for anaesthesia to light touch, pin prick, and temperature. The peripheral nerves should be pal- pated systematically, examining for thickening and tenderness, and peripheral nerve function should be assessed. Histological exam- ination of a biopsy taken from the active edge of a lesion is helpful to support the diagnosis and confirm the classification. The path- ologist should be asked to examine for neural inflammation which will differentiate leprosy from other granulomatous conditions. Serology is not usually helpful diagnostically because antibodies to the species-specific glycolipid PGL-1 are present in 90% of un- treated lepromatous patients but only 40–50% of paucibacillary pa- tients and 5 to 10% of healthy controls. Polymerase chain reaction for detecting M. leprae DNA in skin and nerve biopsies can be a useful confimatory test. Outside leprosy endemic areas, doctors frequently fail to con- sider the diagnosis of leprosy. Of new patients seen from 1995 to 1999 at The Hospital for Tropical Diseases, London, diagnosis had been delayed in over 80% of cases. Patients had been mis- diagnosed by dermatologists, neurologists, orthopaedic sur- geons, and rheumatologists. A common problem was failure to consider leprosy as a cause of peripheral neuropathy in patients from leprosy endemic countries. These delays had serious con- sequences for patients; over one-half of them had nerve damage and disability. Slit skin smears The bacterial load is assessed by making a small incision through the epidermis, scraping dermal material, and smearing evenly onto a glass slide. At least four sites should be sampled (earlobes and edges of active lesions). The smears are then stained

and acid- fast bacilli are counted. Scoring is done on a logarithmic scale per high-power field. A score of 1 + indicates 1 to 10 bacilli in 100 fields, 6 + over 1000 per field. Smears are useful for confirming the diagnosis and should be done annually to monitor response to treatment. Differential diagnosis Doctors should be aware of the normal range of skin colour and texture in their local population, and also of the common endemic skin diseases, such as onchocerciasis, that may coexist or mimic leprosy. Skin The variety of leprosy skin lesions means that a potentially wide range of skin conditions come into the differential diagnosis. At the tuberculoid end of the spectrum, anaesthesia differentiates leprosy from fungal infections, vitiligo, and eczema. At the lepromatous end the presence of acid-fast bacilli in smears differentiates leprosy nodules from onchocerciasis, Kaposi's sarcoma, and post-kala-azar dermal leishmaniasis (Fig. 8.6.28.21). Nerves Peripheral nerve thickening is rarely seen except in leprosy. Hereditary sensory motor neuropathy type III is associated with palpable peripheral nerve hypertrophy. Amyloidosis, which can also complicate leprosy, causes thickening of peripheral nerves. Charcot– Marie–Tooth disease is an inherited neuropathy that causes distal atrophy and weakness. The causes of other polyneuropathies such as HIV, diabetes, alcoholism, vasculitis, and heavy metal poisoning should all be considered where appropriate. Treatment There are six main principles of treatment: 1 Stop the infection with chemotherapy. 2 Treat new nerve damage. 3 Treat reactions. 4 Educate the patient about leprosy. 5 Prevent disability. 6 Support the patient socially and psychologically. These objectives need the patient's cooperation and confidence and can be achieved through the leprosy outpatient clinic with ap- propriate support and patient education. On the first visit there should be a careful assessment of skin and mucosal involvement and accurate evaluation of nerve and eye function. Each patient should be classified using the Ridley–Jopling classification and assessed for evidence of a reaction of new nerve damage. Fig. 8.6.28.21 African woman with facial epidermoid cysts superficially resembling lepromatous leprosy. Copyright D. A. Warrell.

 Chemotherapy All patients with leprosy should be given an appropriate multidrug combination. The first-line antileprosy drugs are rifampicin, clofazimine, and dapsone. The drug combination and duration are determined by the classification of the patient. The WHO has recommended a simple classification for use in the field de- termined only by the number of skin lesions. Patients are clas- sified as paucibacillary if they have up to five skin lesions and as multibacillary if they have six or more skin lesions. In the specialist clinic setting, where skin smears and skin biopsies can be combined with clinical data, patients can be classified into paucibacillary (skin smear-negative TT and BT) and multibacillary (skin smear-positive BT, all BB, BL, and LL). Table 8.6.28.2 gives the drug combinations, doses, and duration of treatment. Patients with multibacillary dis- ease and an initial bacterial index greater than 4 can be treated for 24 months. Rifampicin is a potent bactericide for M. leprae. Four days after a single 600-mg dose, bacilli from a previously untreated patient with multibacillary disease were no longer viable in a mouse footpad test. It acts by inhibiting DNA-dependent RNA polymerase. Because M. leprae can develop resistance to rifampicin as a one-step pro- cess, this drug should always be given in combination with other antileprotics. Dapsone (DDS, 4,4-diaminodiphenylsulphone) is weakly bac- tericidal. Oral absorption is good and it has a long half-life, averaging 28 h. It commonly causes mild haemolysis, but rarely an- aemia. Glucose-6-phosphate dehydrogenase deficiency is seldom a problem. The 'DDS syndrome', which is occasionally seen in leprosy, begins 6 weeks after starting dapsone and manifests as exfoliative dermatitis associated with lymphadenopathy, hepatosplenomegaly, fever, and hepatitis. Clofazimine is a red fat-soluble crystalline dye. The mechanism of its weakly bactericidal action against M. leprae remains un- known. The most

troublesome side effect is skin discoloration, ran- ging from red to purple-black, the degree depending on the drug dose and extent of leprous infiltration (Fig. 8.6.28.22(a) and (b)). The pigmentation usually fades within 6 to 12 months of stop- ping clofazimine, although traces of discoloration might remain for up to 4 years. Urine, sputum, and sweat may become pink. Clofazimine also produces a characteristic ichthyosis on the shins and forearms. Other drugs bactericidal for M. leprae include the fluoroquinolones pefloxacin and ofloxacin, minocycline, and clarithromycin. These agents are now established second-line drugs. Minocycline causes a black pigmentation of skin lesions and so might not be an appropriate substitute for clofazimine if pigmentation is to be avoided. A single-dose triple-drug combination (rifampicin, ofloxacin, and minocycline) has been tested in India for patients with single skin lesions and improved 98% of patients. This regimen can also be used in patients who experience adverse effects of dapsone or clofazimine, even in patients with a high BI. Although the study had major flaws and single-dose treatment is less effective than the conventional 6-month treatment for paucibacillary leprosy, it is an operationally attractive field regimen or for use in patients with peripatetic lifestyles.
Table 8.6.28.2 WHO recommended multidrug therapy regimens Type of leprosy a Drug treatment Monthly supervised Daily self-administered Duration of treatment Paucibacillary Rifampicin 600 mg Dapsone 100 mg 6 months Multibacillary Rifampicin 600 mg Clofazimine 50 mg 12 months Clofazimine 300 mg Dapsone 100 mg a WHO classification for field use when slit skin smears are not available: paucibacillary—up to five skin lesions; multibacillary—more than six skin lesions. (a) (b) Fig. 8.6.28.22 Clofazamine pigmentation in Ethiopian (a) and Peruvian (b) patients. Copyright D. A. Warrell.

8.6.28 Leprosy (Hansen’s disease) 1165 The principal outcome of treatment is improvement of skin le- sions; nerve damage might also improve but to a lesser extent. At the end of a 6-month treatment of borderline disease there may still be signs of inflammation, which should not be mistaken for active infection. Relapse is uncommon with a cumulative relapse rate of 1.07% for paucibacillary leprosy and 0.77% for multibacillary lep- rosy at 9 years after completion of multidrug therapy. M. leprae is such a slow-growing organism that relapse only occurs after many years. M. leprae isolates from relapsed patients who have received multidrug therapy are fully drug sensitive and patients can be re- treated with the same regimen. The distinction between relapse and reaction may be difficult. Since the introduction of multidrug therapy more than 16 mil- lion patients have been treated successfully. Clinical improvement has been rapid and toxicity rare. Monthly supervision of the ri- fampicin component has been crucial to success. Other benefits are reduced deformity rates and increased compliance in control schemes. Reactions may develop months or years after stopping chemotherapy, especially in patients with borderline lepromatous or lepromatous leprosy. It is, therefore, vital when discharging patients to warn them to return should new symptoms appear, especially in hands, feet, or eyes. Patients with reactions or physical or psycho- logical complications will need long-term care. Treatment of new nerve damage Patients with nerve damage present for less than 6 months (assessed by patient history or testing) should receive a 6-month course of steroids starting at a dose of 40 mg prednisolone per day. A random- ized controlled trial has shown that nerve damage present for more than 6 months is not improved by steroid treatment. Management of reactions Awareness of the early symptoms of reversal reactions by both pa- tient and physician is important because, if left untreated, severe nerve damage may develop. The peak time for reversal reactions is in the first 2 months of treatment. Patients should be warned about reactions because the sudden appearance of reactional lesions after starting treatment is distressing and undermines confidence. The treatment of reactions is

aimed at controlling acute inflammation, easing pain, reversing nerve and eye damage, and reassuring the pa- tient. Multidrug therapy should be continued. Type 1 (reversal) reactions Simple anti-inflammatory drugs are rarely sufficient to control symptoms. If there is any evidence of neuritis (nerve tenderness, new anaesthesia, and/or motor loss), corticosteroid treatment should be started. Prednisolone should be given, starting at 40–60 mg/day, re- ducing to 40 mg after a few days, and then by 5 mg every 2–4 weeks. Patients with borderline tuberculoid leprosy in reaction commonly need 4 months of steroids while borderline lepromatous reactions may need 6 months or more. Type 2 (ENL) reactions This is a difficult condition to treat and frequently requires treat- ment with high-dose steroids (80 mg/day, tapered down rapidly) or thalidomide. Since ENL frequently recurs, steroid dependency can easily develop. Thalidomide (400 mg/day) is superior to steroids in controlling ENL and is the drug of choice for young men with severe ENL (Fig. 8.6.28.16). Women with severe ENL might benefit from thalidomide treatment. This is a difficult decision for the woman and her physician and needs careful discussion of the benefits and risks (phocomelia when thalidomide is taken in the first trimester). Women should use double contraception and report immediately if menstruation is delayed. Unfortunately, the problems with thalido- mide mean that it is unavailable in several leprosy endemic countries despite its undoubted value.
A study in Ethiopia showed that pa- tients had a mortality rate of 10% while having ENL, mainly caused by steroid side effects. Clofazimine has a useful anti-inflammatory effect in ENL but takes 6 weeks to become effective and can be used at 300 mg/day for several months. Low-grade chronic erythema nodosum with iritis or neuritis will require long-term suppression, preferably with thalidomide or clofazimine. Acute iridocyclitis is treated with 1% hydrocortisone eye drops given 4 hourly and 1% at- ropine drops twice daily. Neuritis Silent neuritis should be treated similarly to reversal reactions with prednisolone at a dose of 40 mg/day which should be reduced slowly over a period of months. Education of patients Stigmatization due to leprosy occurs worldwide. Patients are fright- ened of social ostracization, physical rejection, and the development of deformities. It is often useful to ask them about their fears so that these can be addressed. They should be reassured that having started treatment they are not infectious to family or friends and can have a sex life. The importance of compliance with antibiotic therapy needs to be emphasized. The patient needs a careful explanation of the diagnosis, aetiology, and prognosis. Prevention of disability The morbidity and disability associated with leprosy is secondary to nerve damage. A major goal in prevention of disability is to create patient self-awareness so that damage is minimized. Monitoring sen- sation and muscle power in patient’s hands, feet, and eyes should be part of the routine follow-up so that new nerve damage is detected early. The patient with an anaesthetized hand or foot needs to under- stand the importance of daily self-care, especially protection when doing potentially dangerous tasks and inspection for trauma. It is helpful to identify for each patient potentially dangerous situations, such as cooking, car repairs, or smoking. Soaking dry hands and feet followed by rubbing with oil keeps the skin moist and supple. An anaesthetized foot needs the protection of an appropriate shoe. For anaesthesia alone, a well-fitting ‘trainer’ with firm soles and shock-absorbing inners will provide adequate protection. Once there is deformity, such as clawing, shoes must be made specially to ensure protection of pressure points and even weight distribution. The patient should be taught to question the cause of an injury so that the risk can be avoided in the future. Plantar ulceration occurs secondary to increased pressure over bony prominences. Ulceration

 is treated by rest. Unlike ulcers in the feet of patients with diabetes or ischaemia, ulcers in leprosy heal if they are protected from weight- bearing. No weight-bearing is permitted until the ulcer has healed. Appropriate footwear should be provided to prevent

recurrence. Physiotherapy exercises should be taught to maximize function of weak muscles and prevent contracture. Contractures of hands and feet, foot drop, lagophthalmos, entropion, and ectropion are amen- able to surgery. Social, psychological, and economic rehabilitation The social and cultural background of the patient determine the na- ture of many of the problems that may be encountered. The patient may have difficulty in coming to terms with leprosy. The community might reject the patient. Education, gainful employment, confidence from family, friends, and doctor, and plastic surgery to correct stig- matizing deformity all have a role to play. Prognosis Most patients, especially those who have no nerve damage at the time of diagnosis, do well on multidrug treatment with resolution of skin lesions. Left untreated, borderline patients will downgrade towards the lepromatous end of the spectrum and lepromatous pa- tients will have the consequences of bacillary invasion. Borderline patients are at risk of developing type 1 reactions, which can result in devastating nerve damage. Treatment of the neuritis is currently unsatisfactory and patients with neuritis might develop permanent nerve damage despite corticosteroid treatment. It is not possible to predict which patients will develop reactions or nerve damage. Nerve damage and its complications can be severely disabling, espe- cially when all four limbs and both eyes are affected. Leprosy in women Women with leprosy are in double jeopardy; not only might they de- velop postpartum nerve damage but also they are at particular risk of social ostracization with rejection by spouses and family. Pregnancy and leprosy There is little good evidence that pregnancy causes new disease or relapse. However, there is a clear temporal association between parturition and the development of type 1 reactions and neuritis when cell-mediated immunity returns to prepregnancy levels. In an Ethiopian study, 42% of pregnancies in borderline lepromatous patients were complicated by a type 1 reaction in the postpartum period. In the same cohort, patients with lepromatous leprosy ex- perienced ENL reactions throughout pregnancy and lactation. ENL in pregnancy is associated with early loss of nerve function compared with nonpregnant individuals. Pregnant and newly de- livered women should have regular neurological examination and steroid treatment instituted for neuritis. Rifampicin, dapsone, and clofazimine are safe during pregnancy. Clofazimine crosses the placenta and babies may be born with mild clofazimine pigmenta- tion. Reactions can be managed with the steroid regimens given here, but with a more rapid reduction in dose. Women should be warned before becoming pregnant of the risk that their condition may de- teriorate after delivery. Ideally pregnancies should be planned when leprosy is well controlled. Prevention and control Leprosy control is now becoming more integrated into general services. Different models of providing leprosy control are used depending on the local facilities. In some endemic countries largely vertical programmes are being retained; in others such as Brazil lep- rosy services are provided within dermatological services. Effective treatment is not merely restricted to chemotherapy but also involves good case management with effective monitoring and supervision and prevention of disabilities. Treating patients with leprosy is a long-term enterprise involving patients, their families, and health workers. Vaccines against leprosy The substantial cross-reactivity between Bacille Calmette–Guérin (BCG) and M. leprae has been exploited in attempts to develop a vaccine against leprosy. Trials of BCG as a vaccine against leprosy in Uganda, New Guinea, Burma, and South India showed it to confer statistically significant but variable protection, ranging from 80% in Uganda to 20% in Burma and this protective effect has been con- firmed in a meta-analysis. A case-control study in Venezuela showed BCG vaccination to give 56% protection to the household contacts of patients with leprosy. Combining BCG and killed M. leprae has been tried, but in both a large population-based trial in Malawi and an immunoprophylactic trial in Venezuela there was no advantage for BCG plus M. leprae over BCG alone. Areas of uncertainty and controversy The optimum duration of treatment is a controversial area. The dur- ation of treatment for multibacillary (MB) patients was

reduced from 24 months to 12 months without good evidence. However, this occurred after the definition of MB patients was broadened and in India up to 60% of MB patients are smear-negative borderline tu- berculoid patients. The concern relates to patients with a high initial bacterial load. Data from India show that patients with a high ini- tial bacterial load (bacterial index >4) treated with 2 years of rifam- picin, clofazimine, and dapsone had a relapse rate of 8/100 person years, whereas patients treated to smear negativity had a relapse rate of 2/100 person years. The dilemma is that since skin smears are abandoned in many programmes those patients in need of longer treatment courses cannot be identified. A new treatment, uniform multidrug treatment (U-MDT), in which all leprosy patients are given 6-months of rifampicin, dapsone, and clofazimine is being tried. The problem is that this regimen adds in clofazimine for many patients who do not need it and will probably be inadequate for the small number of lepromatous leprosy patients with high bacterial loads who also maintain the infection in the community. These

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Revision #1
Created 2026-01-22 16:45:44 UTC by Omar Ayman
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