Guide to diagnosis and management of leprosy

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Conflict of interests: None.

Key words: Leprosy, Hansen's disease, neglected tropical skin disease, multidrug therapy.

Introduction

The claim that leprosy is no longer a public health problem (World Health Organization [WHO] 2005) is wishful thinking.[1] In low- and middle-income countries, patients with leprosy still present regularly at primary healthcare clinics but are often misdiagnosed and/or neglected, as leprosy services have been dismantled and specialized healthcare workers employed in other disciplines.[2] Similar scenarios occur in high-income countries where patients are often diagnosed too late, either because of lack of knowledge and awareness or because of self-stigma and fear of discrimination, leading to unnecessary disabilities and deformities.[3] Leprosy is therefore considered by the WHO as a neglected tropical skin disease.

A patient with leprosy may present with hypopigmented or erythematous macules, with nodules or plaques which are skin coloured, slightly red or hyperpigmented in dark skin. Patients may even have no visible lesions. The patients may complain of loss of sensation in the skin lesions or of the hands or feet. They may have aches and pains in the face or the limbs or mention a numb, sleepy or 'dead' sensation in the affected areas, like 'ants running under their skin'.

It is important to remember that in patients with hypopigmented, erythematous, papular or nodular lesions, the differential diagnosis should include leprosy, particularly in patients in or from endemic areas, as well as pityriasis alba, vitiligo, autoimmune diseases, neurofibromatosis, lymphoma, diabetes and bullous diseases.

Diagnosis

Most important is awareness!! There are three cardinal signs:

1. Loss of sensation in a skin lesion.
2. Enlarged nerves.
3. Positive slit-skin smear (SSS).

To make a definite diagnosis two out of the three cardinal signs are needed. For field settings with limited resources, one clear sign is acceptable as multidrug treatment (MDT) has minimal side-effects and outweighs the potential risk of developing future disabilities.

Loss of sensation: This is tested using a wisp of cotton wool. As loss of light touch is one of the first signs in leprosy, it is recommended not to use a ballpoint or a pin. The area is tested by touching, not swiping. With closed eyes the patient points where he or she is being touched. It is important to make sure the area outside the lesion is tested as well. It is useful to feel the palms of the hands and the soles of the feet for dryness because loss of sweating often presents simultaneously with loss of sensation or may even be detected earlier. Thermal sensitivity, using hot- and cold-water tubes, may be tested as well, but seems less sensitive.

Enlarged nerves: these can be cutaneous nerves or subcutaneous nerves in the vicinity of skin patches or nerve trunks. Palpate at least (Figure 1):

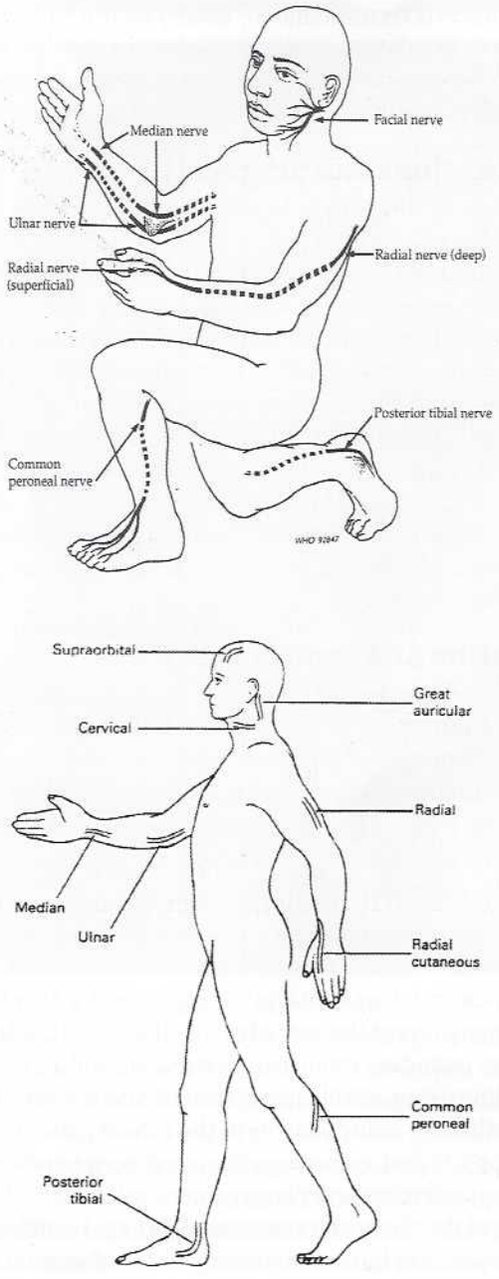

Fig 1. Body diagrams highlighting the anatomical sites of the palpable peripheral nerves that are relevant to examine in clinic. Courtesy of R. Hastings and D. V. A. Opromolla.

- posterior auricular nerves (branches of the facial nerve);
- ulnar nerves;
- median nerves;
- lateral popliteal nerves (also called common peroneal nerves);
- posterior tibial nerves.

You can extend to every palpable nerve. Feel for thickness, consistency and tenderness. Check for sweating, sensory and motor functions of the nerves. Ultrasound, if available, may replace palpation.[4] Simple ultrasound equipment is available today.

Slit-skin smears: These are performed to detect the infectious cause of leprosy: *Mycobacterium leprae* or *M. lepromatosis* through microscopy.[5] These are intracellular, acid-fast bacilli (AFB) that have a predilection for cooler areas of the body (~32°C, e.g. earlobes, chin, buttocks, elbows, knees). SSS is a rapid, relatively easy and low-cost tool to support the diagnosis of leprosy. Samples should be taken from the outer edge of the lesion in macular leprosy and from the centre of a lesion in papular leprosy. A sample from the earlobes, even when no visible lesions are present, is always useful.

The smear is taken while squeezing the skin firmly between the thumb and index finger (or use a pincer) to numb and to diminish the bleeding. Maintain pressure and make an incision into the dermis of about 5 mm long and 2 mm deep. Only tissue fluid is required, as blood will dilute the number of bacilli in the smear (Figure 2). The bacilli are counted and graded according to a logarithmic scale (bacillary index [BI]). In addition, the percentage of solid bacteria considered

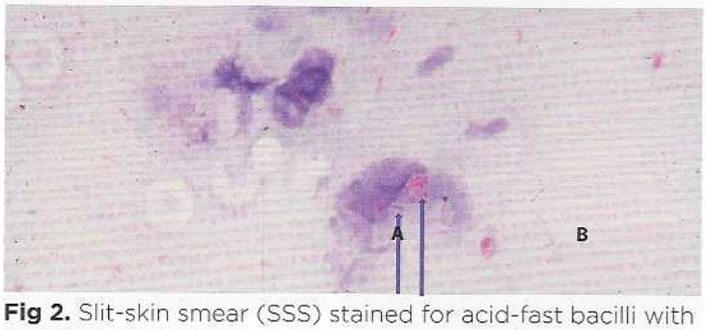

Fig 2. Slit-skin smear (SSS) stained for acid-fast bacilli with modified Ziehl–Neelsen. Arrows: a mycobacterium left and globus (clump of dividing bacteria) right.

living (viable) bacilli is estimated (morphological index [MI]) (Figure 3). It is important to decolorize briefly with 1% hydrochloric acid (10 seconds) in isopropyl alcohol (as in Fite–Faraco stain), as opposed to the more widely available 3% solution, used in the Ziehl–Neelsen stain for tuberculosis (TB). *Mycobacterium leprae* and *M. lepromatosis* are less acid-fast than *M. tuberculosis*, rendering the smear false-negative when using 3% hydrochloric acid. If the preferred 1% hydrochloric acid is not available, a practical answer may be to dilute the 3% solution (based on the authors' experience).

Skin and nerve biopsy: Histopathology can be very helpful in the diagnosis and classification of leprosy, or in the detection of leprosy reactions. It is important to take the skin biopsy from the right place: as with SSS, take the biopsy from the edge of the lesion in tuberculoid (TT) leprosy and from the centre of the lesion in lepromatous leprosy (LL) and use similar staining (Fite–Faraco). Keep in mind that a skin biopsy is taken from

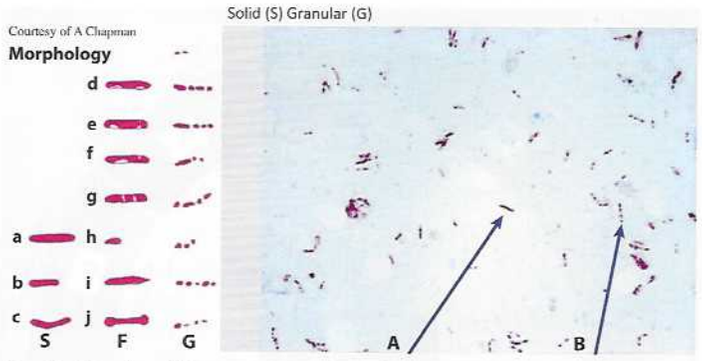

Fig 3. The bacilli are counted and graded according to a logarithmic scale (BI, bacillary index). In addition, the percentage of solid bacteria is estimated (MI, morphological index). Morphology S: solid (live); F: fragmented (h, I, j: most likely artefacts); G: granular (dead); A: solid bacterium and B: a granular bacterium. Courtesy of A. Clapasson.

only one area of the body and may not represent the whole spectrum.

Pure neural leprosy can be diagnosed by a nerve biopsy taken from a small cutaneous or subcutaneous nerve. From a larger nerve, a fine-needle aspiration can be done for cytology and bacteriology with polymerase chain reaction (PCR).

Laboratory tests: These can be of help in the diagnosis and classification of leprosy. Another way to detect bacilli in a smear is through PCR. This is a more sensitive technique than the AFB staining technique,[6] but may still be negative in patients with paucibacillary (PB) leprosy. SSS and immunological (serology and techniques to detect cellular immunoreactivity)[7] and molecular (PCR) techniques are useful in the diagnosis of multibacillary (MB) leprosy, in the follow-up and in the detection of relapses.

The antibody titre against phenolic glycolipid 1 (PGL-1), a cell wall species-specific glycolipid, is a useful test in MB leprosy. However, this test may be positive in contacts and negative in PB leprosy. It helps to classify leprosy into PB and MB, and it can be used to follow the effect of treatment in patients with MB and to detect relapses.[8] It is extensively used in Brazil and several programmes elsewhere. The value of the recently introduced antibody test with synthetic LID-1 seems to add little additional information.

Leprosy remains a clinical diagnosis: the clinician should take everything into account, particularly the clinical symptoms, to make the diagnosis and classification.

The clinical spectrum of leprosy is determined by the host immune response

It is the cell-mediated immunity (CMI) that determines the clinical spectrum of the disease in patients who develop leprosy. The Ridley–Jopling scale is useful to stratify according to CMI and to predict complications (Figure 4).[9] It consists of the polar tuberculoid (TT) form at one end of the spectrum (Figure 5a, b), consisting of a single well-described skin lesion or an enlarged nerve without detectable bacilli and a high CMI against *M. leprae/lepromatosis* antigenic determinants, and on the other side of the spectrum the polar lepromatous (LL)

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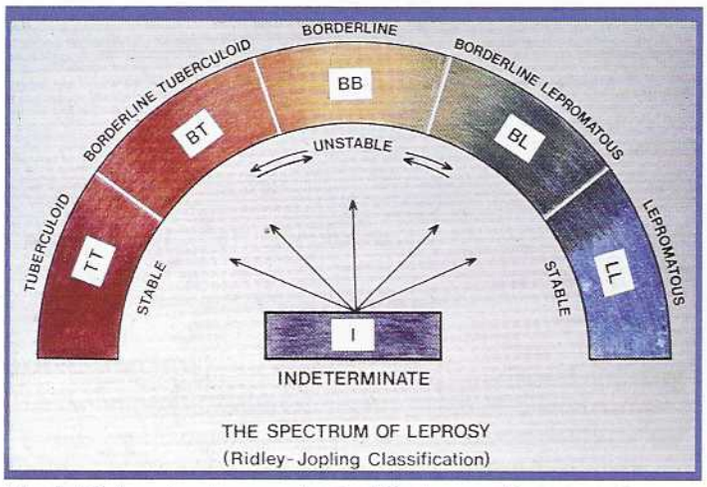

Fig 4. Ridley–Jopling scale stratified according to cell-mediated immunity. Courtesy of D. L. Leiker.

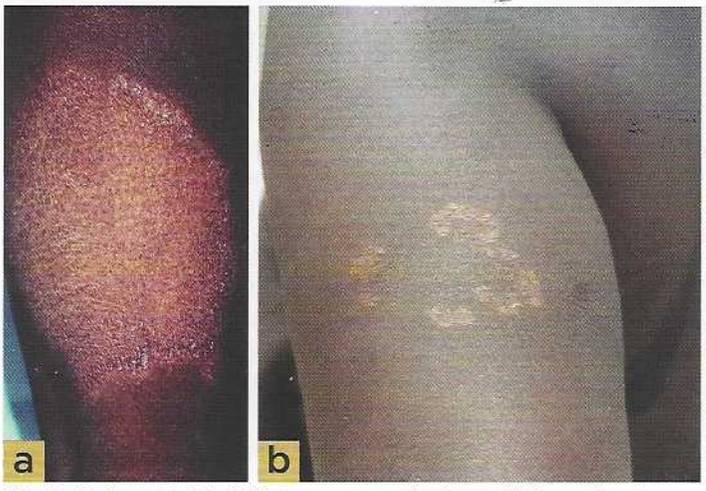

Fig 5. Tuberculoid (TT) leprosy; a single well-described lesion with a healing centre. **(a)** A still slightly hypopigmented centre. **(b)** The centre heals so quickly that the rim has disappeared, and the centre stays skin coloured. **(a)** Courtesy of D. L. Leiker.

leprosy with nodules and/or plaques (Figure 6a, b), with more or less symmetrically enlarged nerves or only an infiltrated skin with numerous bacilli and a lack of CMI against *M. leprae/lepromatosis* antigenic determinants. Lepra bonita (also referred to as beautiful leprosy) is a rare form of LL leprosy in which the skin is diffusely infiltrated so that natural wrinkles disappear, and the skin becomes shiny (Figure 7). These polar groups are stable and do not change classification.

In between these polar groups are the borderline groups, comprising most patients. Patients in this group may change their classification. They may 'upgrade' (become more tuberculoid) or 'downgrade' (become more lepromatous). This may occur without many symptoms or with symptoms during a 'reaction'. Borderline tuberculoid (BT) (Figure 8) has predominantly tuberculoid features and borderline lepromatous (BL) (Figure 9a, b) has predominantly lepromatous features. Between these two types is a small group of mid-borderline (BB) leprosy (Figure 10). These patients typically have dome-shaped and/or punched-out skin lesions in which the centre is not involved. The involved border may be wavy. In some patients it is not possible to classify the

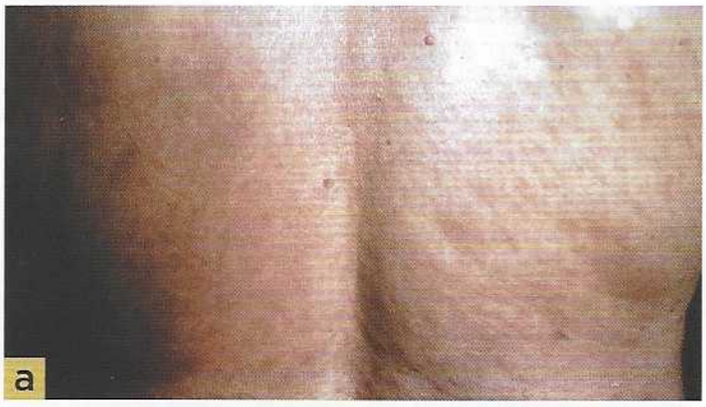

Fig 6. Lepromatous leprosy (LL). **(a)** Infiltrated plaques; **(b)** nodules.

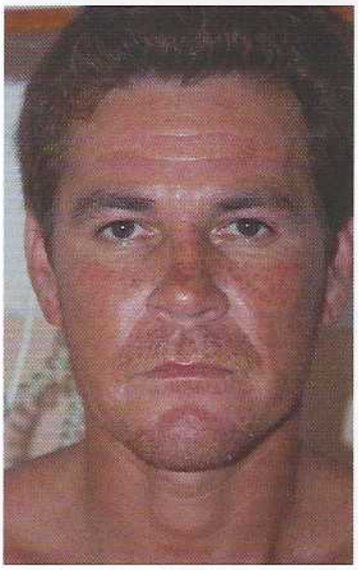

Fig 7. Lepra bonita. The skin is shiny and the patient looks much younger than they are. There is hardly anything to see, only with palpation you may feel some induration.

type of leprosy when the lesions are clinically and histologically indeterminate (indeterminate leprosy [IL]). IL (Figure 11) is either an early stage of the disease, which usually resolves on its own, or may progress into one of the types described in the Ridley–Jopling classification, depending on the development of the CMI. Another challenging group to classify is pure neural leprosy in which there is no involvement of the skin. The frequency of this type can vary from 1% to 10%, depending on the geographical area and awareness of clinicians.

For practical purposes in the field, the WHO has

classified leprosy into two groups based on the number of skin lesions: PB leprosy includes one to five skin lesions and a negative SSS; MB leprosy is classified as six or more skin lesions, or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis), or with a positive SSS irrespective of the number of lesions.[8] Although this is a very practical approach, several reports have shown that by just counting lesions, up to 30% of patients are incorrectly classified as PB and therefore under-treated.[10]

It must be emphasized that leprosy is an infectious disease leading to an immunological disease and when not treated properly leads to deformities and disabilities.

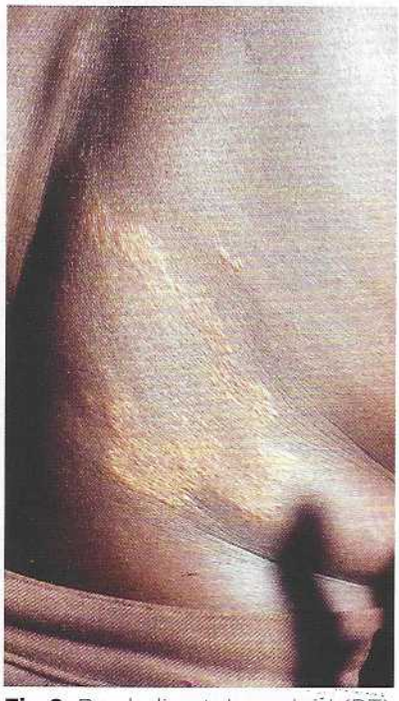

Fig 8. Borderline tuberculoid (BT) leprosy; the rim edge is streaming and there is central healing. There are satellite lesions.

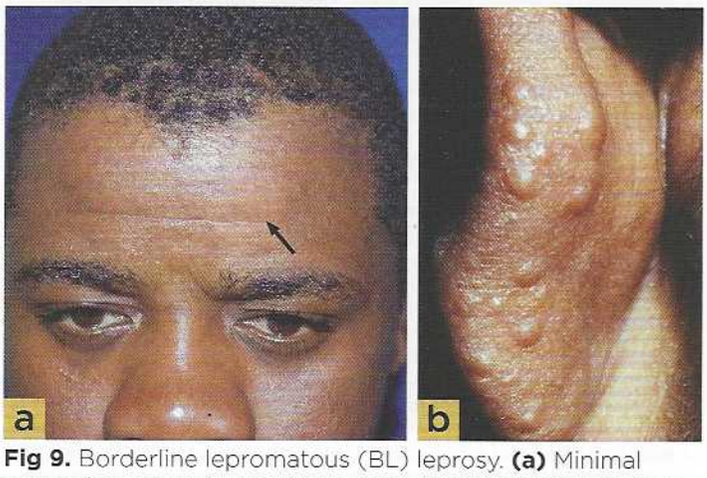

Fig 9. Borderline lepromatous (BL) leprosy. **(a)** Minimal somewhat coppery lesions that may have loss of sensation (arrow). **(b)** Small papules in colder areas, particularly the ears.

Treatment

MDT consists of a combination of two or three drugs depending on the type of leprosy. MDT is widely available and effective and provided free of charge through the WHO. However, monthly drug pick-ups may be a financial burden for some patients, threatening drug compliance.

PB leprosy: 600 mg rifampicin once monthly for 6 months under supervision and daily 100 mg dapsone, unsupervised. The dose is for a 60 kg patient. To be allowed to discontinue the treatment six supervised monthly doses should be given in 9 months (Table 1).[11]

MB leprosy: 600 mg rifampicin and 300 mg clofazimine once monthly under supervision and 100 mg dapsone and 50 mg clofazimine daily, unsupervised. The WHO guidelines advise that 12 supervised monthly doses should be given within an 18-month period.[8] The listed dosages are for patients weighing 60 kg or more (Table 1).

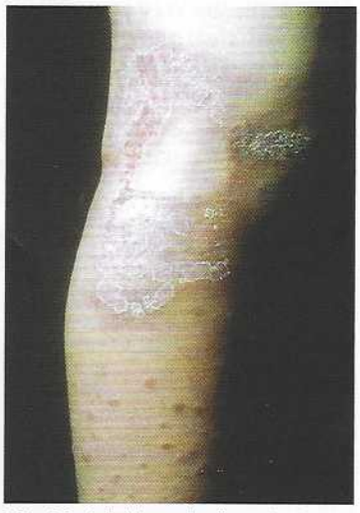

Fig 10. Mid-borderline (BB) leprosy. Typically round and gyrate lesions with uninvolved centre and small dome-shaped nodules. Courtesy D. L. Leiker.

Fig 11. Indeterminate leprosy. Hardly any hypopigmentation visible. There may be or may not be a minimal loss of sensation. Over time, unlike pityriasis alba, the lesions do not change place but may enlarge or resolve.

Table 1. Multidrug treatment regimen as advised by the World Health Organization[8]

Age group	Drug	Dosage and frequency	Duration (months)	
			PB	MB
Adult	Rifampicin	600mg once a month	6	12
	Dapsone	100mg daily		
	Clofazimine	300mg once a month, 50mg daily	-	
Children: 10–14 years old	Rifampicin	450mg once a month	6	12
	Dapsone	50mg daily		
	Clofazimine	150mg once a month, 50mg daily	-	
Children: <14 years old or <40 kg	Rifampicin	10mg/kg once a month	6	12
	Dapsone	2mg/kg daily		
	Clofazimine	6mg/kg once a month, 1mg/kg daily	-	

MB, multibacillary; PB, paucibacillary.

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At present, the WHO is considering uniform MDT (UMDT), a 6-month treatment package for all leprosy classifications (PB and MB), including all three forementioned drugs. The advantage would be that in field settings a distinction in the type of leprosy is no longer needed and undertreatment is prevented. However, this strategy is questioned as many patients will unnecessarily receive clofazimine causing side-effects, e.g. hyperpigmentation that may increase stigmatization and discrimination. At the same time, UMDT is considered too short for treating MB leprosy. Patients will be at increased risk of developing reactions consequently leading to a rise in disabilities and deformities.

MDT has proved to be sturdy; the relapse rate has been very low,[12] although in MB leprosy, relapses may occur 6–10 years after treatment release and most studies have limited follow-up.[12] Overall, MDT is relatively safe and well accepted. Dapsone may cause (severe) haemolytic anaemia in patients deficient in glucose-6-phosphate dehydrogenase (G6PD).[10] Asian populations (e.g. China, Thailand, Nepal, Indonesia) have a higher risk of developing dapsone hypersensitivity syndrome, a drug reaction with eosinophilia and systemic symptoms (DRESS), which is associated with HLA-B*13:01.[13–15] It is important to discuss the most common side-effects with patients, prior to MDT initiation.

In patients intolerant of either dapsone or clofazimine, two drugs (one of which is rifampicin) are used as in many settings alternative regimens are not available or affordable.

Alternative combinations like rifampicin, ofloxacin and minocycline (ROM) are suggested to give equivalent outcomes in the treatment of leprosy, although some studies have reported it to be less effective than MDT.[16–18]

Recurrence: After treatment the disease may recur because of undertreatment, drug resistance, persistence or new infections. In general, the recurrent episode is sensitive to the original MDT, but resistance to dapsone, rifampicin and ofloxacin has been demonstrated for which PCR testing is available.[19] Resistance to clofazimine is never convincingly proven. In cases of resistant *M. leprae*, depending on the type of resistance, the WHO recommends MDT with three drugs, as in Table 2, and potentially, in the future, bedaquiline.[20,21] Before, during and after MDT immune reactions and nerve damage may occur. These will be discussed in a follow-up paper.

Acknowledgements

Many thanks to the patients who agreed their pictures could be used for teaching purposes.

References

1. Naafs B. Viewpoint: leprosy after the year 2000. *Trop Med Int Health* 2000; **5**:400–3.
2. da Costa Nery JA, Schreuder PA, de Mattos PC *et al.* Hansen's disease in a general hospital: uncommon presentations and delay in diagnosis. *J Eur Acad Dermatol Venereol* 2009; **23**:150–6.
3. Lockwood DN, Reid AJ. The diagnosis of leprosy is delayed in the United Kingdom. *QJM* 2001; **94**:207–12.
4. Jain S, Visser LH, Suneetha S. Imaging techniques in leprosy clinics. *Clin Dermatol* 2016; **34**:70–8.
5. [No authors listed.] WHO guidelines for skin smears. *Int J Lepr Other Mycobact Dis* 1987; **55**:421–2. http://ijl.ilsl.br/detalhe_artigo.php?id=MTcwOQ%3D%3D&secao=WHO+GUIDELINES+FOR+SKIN+SMEARS
6. Mohanty PS, Naaz F, Bansal AK *et al.* Molecular detection of *Mycobacterium leprae* using RLEP-PCR in post elimination era of leprosy. *Mol Biol Res Commun* 2020; **9**:17–22.
7. de Souza VN, Iyer AM, Lammas DA *et al.* Advances in leprosy immunology and the field application: a gap to bridge. *Clin Dermatol* 2016; **34**:82–95.
8. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. Available at: https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf (last accessed 11 July 2022).
9. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis* 1966; **34**:255–73.
10. Alemu Belachew W, Naafs B. Position statement: LEPROSY: diagnosis, treatment, and follow-up. *J Eur Acad Dermatol Venereol* 2019 Jul; **33**:1205–13.
11. Gelber RH, Grosset J. The chemotherapy of leprosy: an interpretive history. *Lepr Rev* 2012; **83**:221–40.
12. Lockwood DNJ, Butlin CR, Penna GO. Current leprosy multi-drug treatment duration for MB patients (12 months) produces good clinical outcomes over many years; *Lepr Rev* 2021; **92**:97–101.
13. Krismawati H, Irwanto A, Pongtiku A *et al.* Validation study of HLA-B*13:01 as a biomarker of dapsone hypersensitivity syndrome in leprosy patients in Indonesia. *PLoS Negl Trop Dis* 2020; **14**:e0008746.
14. Wang N, Parimi L, Liu H, Zhang F. A review on dapsone hypersensitivity syndrome among Chinese patients with an emphasis on preventing adverse drug reactions with genetic testing. *Am J Trop Med Hyg* 2017; **96**:1014–18.
15. Zhang F-R, Liu H, Irwanto A *et al.* HLA-B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med* 2013; **369**:1620–8.
16. Lazo-Porras M, Prutsky GJ, Barrionuevo P *et al.* World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy: a systematic review and meta-analysis. *BMC Infect Dis* 2020; **20**:62.
17. Lockwood DNJ, Da Graca Cunha M. Developing new MDT regimens for MB patients; time to test ROM 12 month regimens globally. *Lepr Rev* 2012; **83**:241–4.
18. Setia MS, Shinde SS, Jerajani HR, Boivin JF. Is there a role for rifampicin, ofloxacin and minocycline (ROM) in the treatment of leprosy? Systemic review and meta-analysis. *Trop Med Int Health* 2011; **16**:1541–51.
19. Araujo S, Goulart LR, Truman RW *et al.* qPCR-High resolution melt analysis for drug susceptibility testing of *Mycobacterium leprae* directly from clinical specimens of leprosy patients. *PLoS Negl Trop Dis* 2017; **11**:e0005506.
20. ClinicalTrials.gov. A study to evaluate the efficacy and safety of bedaquiline (TMC207) in participants with multibacillary leprosy. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03384641?cond=Leprosy&rank=10 (last accessed 11 July 2022).
21. Ji B, Chauffour A, Andries K, Jarlier V. Bactericidal activities of R207910 and other newer antimicrobial agents against *Mycobacterium leprae* in mice. *Antimicrob Agents Chemother* 2006; **50**:1558–60.

Table 2. Alternative regimens in case of drug resistance to rifampicin and rifampicin plus ofloxacin according to World Health Organization guidelines

Resistance type	Drug alternatives	
	First 6 months (daily)	Next 18 months (daily)
Rifampicin resistance	Levofloxacin 500mg + minocycline 100mg + clofazimine 50mg	Levofloxacin 500mg OR minocycline 100mg + clofazimine 50mg
	Levofloxacin 500mg + minocycline 500mg + clofazimine 50mg	Levofloxacin 500mg + clofazimine 50mg
Rifampicin plus ofloxacin resistance	Clarithromycin 500mg + minocycline 100mg + clofazimine 50mg	Clarithromycin 500mg OR minocycline 100mg + clofazimine 50mg

Of note. Levofloxacin 500 mg, ofloxacin 400 mg and moxifloxacin 400 mg may be interchanged depending on resistance profiles and availability.