250 Leprosy (*Mycobacterium leprae*)

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SHORT VIEW SUMMARY

Epidemiology

- Leprosy is an underrecognized and underdiagnosed disease. Early diagnosis is key to decreasing disability at the individual level, and decreasing risk of *Mycobacterium leprae* transmission in the community.
- Of the people who were diagnosed with leprosy in 2016, 95% were from only 22 countries.
- Experts hypothesize that most of the world's population has a natural immunity to *M. leprae,* although the factors that make some people more susceptible are incompletely understood.
- The primary route of transmission is likely by the respiratory route, either from respiratory droplets or nasal secretions.
- Nine-banded armadillos in the southeastern United States carry *M. leprae,* and genetic epidemiology studies suggest zoonotic transmission.

Microbiology

- *M. leprae* is an obligate intracellular pathogen with tropism for macrophages and Schwann cells. It cannot be propagated in culture.
- *M. leprae* is acid-fast positive. The best staining method to detect *M. leprae* in human specimens is the Fite stain.
- *M. leprae* can stain acid-fast positive even when they are no longer viable, although the morphology and staining characteristics change (see Fig. 250.5).

Diagnosis (Fig. 250.3)

- On clinical examination, leprosy skin lesions can be macules, papules, nodules, or patches. Classically, the skin lesions have decreased touch sensation.
- Nondermatologic symptoms can include uveitis, neuritis, nasal septal perforation, and paresthesias in hands or feet.
- A person with hypoesthesia may present with burns, ulcers, or other traumatic lesions and a report of not having felt the injury.
- *M. leprae* infection is confirmed by histopathology and Fite staining of biopsy material. The biopsy should be full thickness, including the deep dermis.
- The leprosy subtype should be determined using the Ridley-Jopling criteria.
- Assistance is available from the US National Hansen's Disease Program (NHDP) in Baton Rouge, LA.

Therapy (Table 250.1)

- *M. leprae* infection is not an indication for isolation of people with leprosy in any clinical form or at any stage of disease.
- Care for people with leprosy is with standard precautions.
- By the US NHDP guidelines, people with paucibacillary leprosy receive dapsone and rifampicin. People with multibacillary leprosy receive dapsone, rifampicin, and clofazimine.
- Alternative antibiotics that can be substituted for components of recommended multidrug therapy include clarithromycin, ofloxacin, and minocycline.
- If a person develops neuritis, reversal reaction, or erythema nodosum leprosum during multidrug therapy, the antibiotics should be continued.
- Treatment for neuritis with or without associated reversal reaction is with high-dose corticosteroids.
- Treatment options for erythema nodosum leprosum include thalidomide (with appropriate precautions for dispensing this teratogenic agent), high-dose clofazimine, and corticosteroids.

Prevention

- Bacillus Calmette-Guérin (BCG) vaccination of household contacts of people with leprosy may decrease the risk of developing clinical disease. If a contact does develop leprosy after BCG vaccination, vaccination decreases the chance that the leprosy will be multibacillary.
- Studies on single-dose rifampicin prophylaxis of contacts of people with leprosy have been inconclusive. It is part of the WHO guidelines but has not been adopted by the US NHDP as of this writing.

Leprosy, or Hansen disease, is a curable infectious disease caused by *Mycobacterium leprae*. Widespread implementation of multidrug antibiotic therapy for leprosy in the 1980s dramatically decreased the burden of leprosy worldwide. There is no indication for physical or social isolation of people with leprosy. Sequelae of leprosy, including nerve damage, muscle weakness, and physical deformity, are related to delayed diagnosis and pathologic immune reactions that complicate the course of disease. Early diagnosis and prompt initiation of multidrug therapy are crucial for improving outcomes for people with leprosy.

HISTORY AND SOCIETY

Descriptions of leprosy have been found in texts written over 2000 years ago in China, India, and Egypt.[1,2] Skeletal remains from centuries ago show bony changes consistent with leprosy and *M. leprae* DNA is detectable in skeletal remains from the 4th century. Genetic epidemiology studies show correlation of leprosy strain types with patterns of human migration and trade routes, and confirm the ancient origin of this bacterium.[3]

M. leprae was discovered in 1873 by Gerhard Henrik Armauer Hansen in Norway, in a time when leprosy incidence was increasing. Hansen visualized bacteria in tissue from a nodule, but was unable to culture the bacteria or infect animals, which would have been proof of disease causation. Hansen inoculated the eye of a leprosy patient with a knife that had incised a leprous nodule from another patient. He admitted doing this without her consent, and lost physician privileges but remained the Chief Medical Officer for Leprosy in Norway.[4]

Fear of leprosy led to compulsory isolation of people suspected to have leprosy. There is no indication for isolation of people with leprosy at any stage of disease.[5] The current goals of the World Health Organization (WHO) for 2020 are zero new cases of leprosy in children where deformity is present at diagnosis, reduction in the rate of leprosy with disability at diagnosis in all ages, and zero countries with laws permitting discrimination against leprosy ("Triple Zero Campaign").[6] WHO guidelines for eliminating discrimination against people with leprosy recommend that discriminatory language, including the term *leper,* be removed from government publications. *Leper* is a stigmatizing term and should not be used to refer to someone with *M. leprae* infection.[5]

EPIDEMIOLOGY

Leprosy is an underrecognized and underdiagnosed disease. Challenges to prompt diagnosis include reluctance of patients to seek care because of leprosy-related stigma and failure of physicians to recognize the

disease at the time of clinical presentation. Additionally, there are no definitive laboratory tests to determine who has had exposure, has infection, or is at risk for progressing from infection to clinical leprosy. Experts hypothesize that most of the world's population has a natural immunity to leprosy, and it is unknown what factors make some people more susceptible to *M. leprae* infection and subsequent development of clinical leprosy. The prolonged incubation periods between exposure, infection, and development of symptoms are challenging for studies of *M. leprae.*

Studies on *M. leprae* transmission are also limited by the inability to propagate *M. leprae* in culture and the lack of an animal model that replicates human leprosy and leprosy pathologic immune reactions. It is thought that transmission occurs with close, long-term exposure from a person with a disseminated leprosy to a person who has an innate susceptibility to the infection. The primary mode of transmission is thought to be by the respiratory route, from either respiratory droplets or nasal secretions.

Rees and McDougall showed that athymic mice could be infected with *M. leprae* when the respiratory exposure was 60 minutes to *M. leprae* aerosolized in a 1.2×10^8 *M. leprae*/mL suspension. Even in a laboratory setting with high concentrations of *M. leprae,* only 33% of mice had any tissues positive for *M. leprae* 14 to 24 months after exposure.[7] *M. leprae* DNA is detectable in the nasal secretions of people with leprosy and in those who live in leprosy-endemic areas, but the role of this carriage in transmission has not been definitively established.[8] After respiratory introduction of *M. leprae,* the bacteria likely disseminate throughout the body. One hypothesis is that this is due to reprogramming of infected cells into stem cells, which migrate and affect immune response.[9] In untreated lepromatous leprosy with high bacillary load, *M. leprae* bacteremia can be detected.[10]

Antibodies to *M. leprae* have been detected in cord blood, although *M. leprae* bacteremia in cord blood has not been reported.[11] Studies of placentas from mothers with lepromatous leprosy do not show pathologic changes associated with leprosy, although small numbers of acid-fast bacilli (AFB) have been found in placental tissues.[12] Thus vertical transmission of leprosy from a mother with lepromatous leprosy is possible, but extremely unlikely if she has been treated. Skin-to-skin contact as a route of transmission has not been confirmed.[13] Multiple publications have reported leprosy lesions developing in the area of a tattoo, suggesting inoculation leprosy from unsterilized needles.[14]

Genetic Epidemiology

Leprosy cases can be clustered within communities and families. A series of studies have been conducted looking for a genetic explanation for susceptibility to leprosy. Early genetic linkage studies from Brazil reported associations of human leukocyte antigen (HLA) class II and tumor necrosis factor (TNF) genes and a cluster of genes at chromosome 17q11.2 with leprosy.[15,16] A genome-wide association scan in Han Chinese found five genes associated with susceptibility to leprosy: *TNFSF15, HLA-DRB1, RIPK2, NOD2,* and *LRRK2.*[17] Single nucleotide polymorphism (SNP) types in the *NOD2* pathway have been found to be associated with leprosy in several populations.[18,19] An additional chromosome location found to be associated with leprosy was chromosome 6q25, in which risk alleles in the Parkinson disease gene *PARK2* were associated with risk of leprosy in Vietnamese and Brazilian populations.[20,21] There are no confirmed SNPs associated with a person's risk of developing either multibacillary or paucibacillary leprosy; a review of genetic studies that address these designations has been compiled by Gaschignard and colleagues.[22]

Zoonotic Potential

There are several animal reservoirs for *M. leprae.* Nine-banded armadillos (*Dasypus novemcinctus*) are a probable source of leprosy in the southeastern United States. A strain of *M. leprae* circulating in armadillos from at least four different states is identical to the *M. leprae* strain in people with leprosy in these states who never traveled outside the United States.[23] Additionally, a new armadillo-related *M. leprae* strain has been identified in both armadillos and humans. A recent study found that over 40% of people with leprosy referred to the US National Hansen's Disease Program (NHDP) for leprosy diagnosis in 2007 to 2012 had one of two armadillo-associated strains.[24] Genetic typing suggests that these armadillo-associated strains were introduced into North America during migrations from Europe.

Recently, leprosy in red squirrels (*Sciurus vulgaris*) from Scotland and England has been described. The causative bacterium for squirrel leprosy in England is *M. leprae.* This *M. leprae* is closely related to *M. leprae* from a human skeleton buried 700 years ago in Britain, as well as to *M. leprae* in US armadillos.[25] In Scotland red squirrels, *M. lepromatosis* has been isolated as the cause of squirrel leprosy. There are no reported transmissions of leprosy from red squirrels to humans in either of these countries.[25] Non–experimentally acquired leprosy has also been described in chimpanzees and macaques.[26,27]

There are no known insect vectors that transmit *M. leprae.* A recent study showed experimental infection of the kissing bug *Rhodnius prolixus* with transmission of infection to the mouse footpad by *R. prolixus* feces,[28] but this has yet to be replicated and is an area for further investigation. Molecular studies have detected *M. leprae* DNA from soil and water, and water-based organisms have been experimentally infected with *M. leprae.* Lymphocyte-free *rag1* mutant zebrafish form granulomas after experimental *M. leprae* infection.[29] Currently, there is no strong evidence supporting an environmental source for transmission of *M. leprae* to humans.[30]

Nosocomial Infections

People who are caring for a person with *M. leprae* infection should use standard precautions.[31] There is no indication for contact or respiratory isolation precautions for people with treated or untreated leprosy. Persons treated with multidrug therapy become noninfectious in a matter of days.[32]

Global Epidemiology

The adoption of multidrug therapy for leprosy in 1981 dramatically decreased the rate of leprosy new case detection worldwide. In 2016, the WHO reported 214,783 new cases of leprosy diagnosed worldwide, a new case detection rate of 2.9 per 100,000 population (Fig. 250.1); 22 countries accounted for 95.03% of new cases. The greatest number of cases are reported from India (63%), Brazil (12%), and Indonesia (8%). Six percent of new cases already have severe disability with visible deformity, an indicator of significant delay in diagnosis.[6] Millions of people worldwide are living with sequelae of leprosy.

Leprosy is an underdiagnosed disease.[33] This is related to the chronic nature of the infection with insidious onset of symptoms, fear and stigma deterring contact with the health care system, or delay in diagnosis when signs and symptoms are not identified as being compatible with leprosy. In places with endemic leprosy, active case-finding activities diagnose more leprosy than would be expected from the baseline new case detection rate. Delay in diagnosis results in increased physical and functional disability from further nerve damage. Delay in diagnosis may also increase risk of transmission of *M. leprae* from someone with multibacillary leprosy with a high bacterial index. Awareness among medical professionals and communities is essential for timely diagnosis and initiation of treatment.

Epidemiology in the United States

Since 1894, 13,950 cases of leprosy have been registered in the United States. The NHDP estimates that approximately 9000 people who have or had leprosy are alive, many with long-term sequelae of leprosy and who could benefit from specialized care. There were 178 new cases reported in 2015, which continues a trend of increased case reporting. Most cases were reported from Florida, California, Texas, Louisiana, Hawaii, and New York. Fig. 250.2 shows the distribution of reported leprosy cases from 2005 to 2014. There are "indigenous foci" of leprosy transmission in Hawaii, Puerto Rico, and the region of the western Gulf of Mexico. There were 96 cases reported from Texas, Louisiana, Arkansas, Mississippi, Alabama, Georgia, and Florida. These are states where *M. leprae* has been isolated from nine-banded armadillos; 65% of cases from these states were in people who were born in and had never lived outside the United States. Country-wide, 57% of people with leprosy reported being born outside of the United States, with most cases in people coming from the South Pacific region. In 2015, new cases ranged

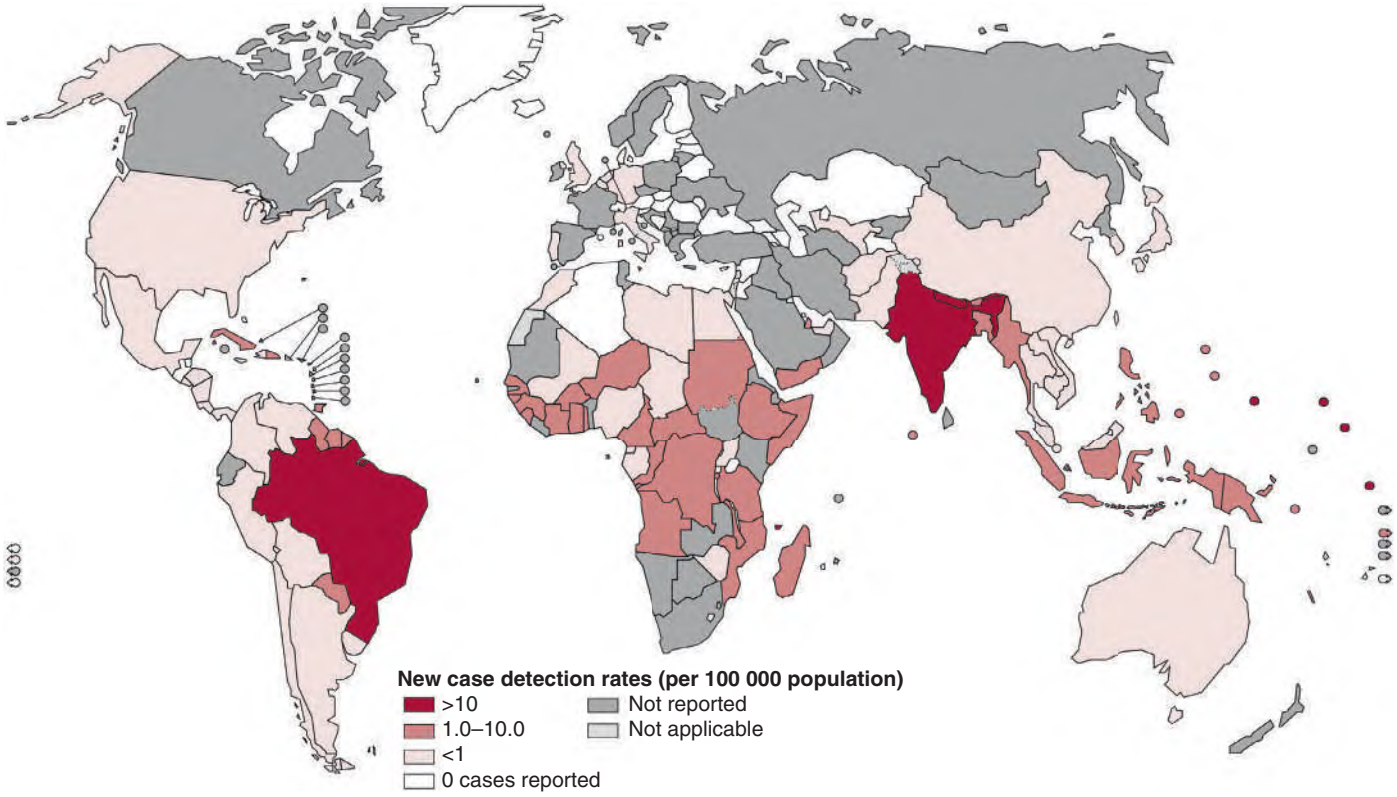


FIG. 250.1 Geographic distribution of new cases of leprosy diagnosed in 2016. *(From World Health Organization. Global leprosy update, 2016: accelerating reduction of disease burden.* Wkly Epidemiol Rec. *2017;92:501–519; reprinted with permission.)*

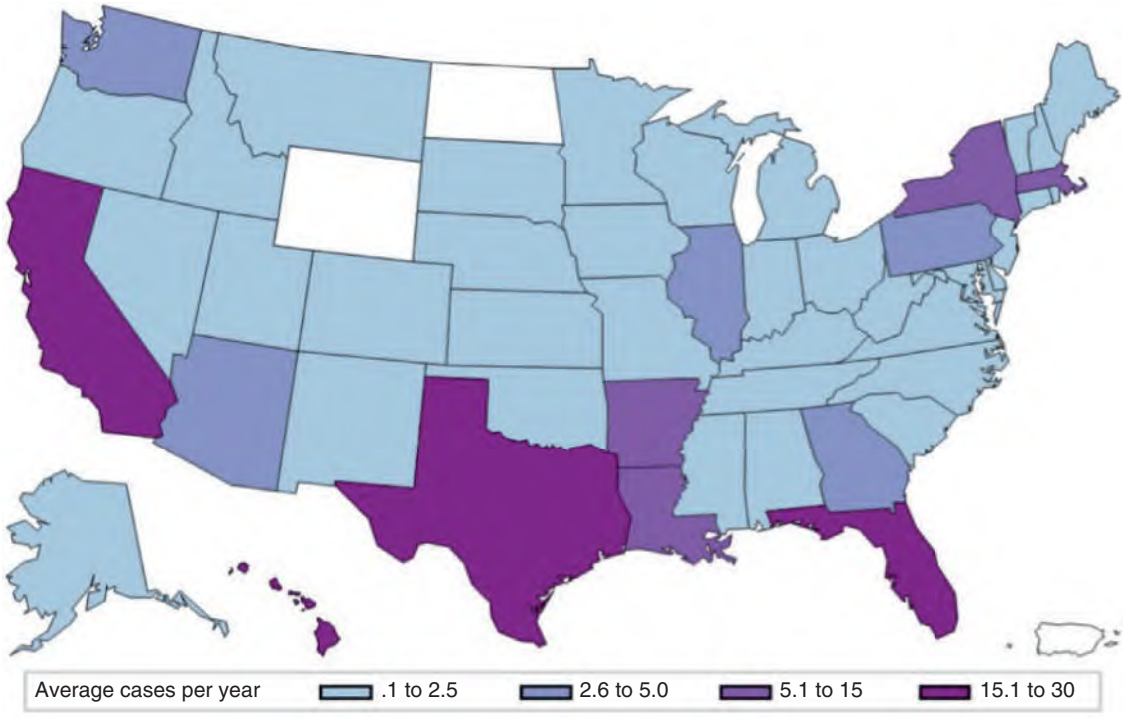


FIG. 250.2 Average number of new cases of leprosy diagnosed per year (2005–2014) in the United States. *(Reprinted with permission from the US Human Resources and Services Administration. Originally published as Figure 3 in* A Summary of Hansen's Disease in the United States—2015.*)*

in age from 7 to 95 years and were 66% male. Over half of new cases had lepromatous leprosy, the most disseminated form of leprosy, which increases risk for complications and sequelae.[34]

MICROBIOLOGY

M. leprae is not culturable on standard laboratory growth media. Isolation and propagation of *M. leprae* in the laboratory requires experimental infection of armadillos or footpads of immunodeficient mice.[35] The doubling time of *M. leprae* is 14 days during the logarithmic growth phase, and up to 40 days during mouse footpad infection.[36] *M. leprae* are Gram stain positive and carbol fuschin acid-fast stain positive. They are straight or slightly curved, 2.1 µm long, and 0.25 to 0.3 µm in width. The cell wall of *M. leprae* is rich in lipids and glycolipids, including phenolic glycolipid 1 (PGL-1). Antibody to PGL-1 is used to assess exposure to *M. leprae* and sometimes as part of diagnostic evaluation. There is no evidence of plasmids or bacteriophages that contribute to *M. leprae* pathogenesis.

M. leprae is an obligate intracellular pathogen, with macrophages and Schwann cells most frequently infected. The genome of *M. leprae* is much smaller than *Mycobacterium tuberculosis* (3.27 vs. 4.41 Mb, respectively), and appears to have undergone reductive evolution with loss of portions of the oxidative, microaerophilic, and anaerobic respiratory chains, such that it is unable to utilize certain carbon sources.[37] Protein-coding genes comprise only half of the *M. leprae* genome.[37] The *M. leprae* cell wall components are less diverse than in *M. tuberculosis,* and *M. leprae* has fewer enzymes available to facilitate scavenging of host cell lipids.[37] It lacks many of the enzymes used by *M. tuberculosis* to survive in macrophages.[37] *M. leprae* has an extremely conserved genome, with 99.995% sequence identity in *M. leprae* strains from four geographically distant countries.[3] The frequency of SNPs is very low at 1 in 28,400 base pairs. A survey of 84 SNPs in *M. leprae* from 28 geographic regions separate *M. leprae* into 4 SNP types and 16 SNP subtypes.[1,3] These SNP subtypes have been used for phylogeographic studies charting the dissemination of leprosy with human migration routes throughout history.

Recently, a new species of mycobacteria, *M. lepromatosis,* has been implicated as a cause of leprosy in humans. It is reported to have association with diffuse lepromatous leprosy, and with erythema necroticans, also known as Lucio phenomenon, a potentially fatal complication of leprosy.[38] *M. lepromatosis* was first characterized in two patients from Mexico who had diffuse lepromatous leprosy and erythema necroticans that was fatal.[39] In one study, 6 of 227 leprosy biopsies collected worldwide had *M. lepromatosis*; all were from people from Mexico.[40] *M. lepromatosis* has also been identified in red squirrels in the United Kingdom that had leprosy-like syndromes.[25,41] *M. lepromatosis* and *M. leprae* genomes are similar sizes and have 93% nucleotide sequence identity in protein-coding genes, but only 82% in pseudogenes. To date, no mutations have been identified in *M. lepromatosis* that correspond to drug resistance mutations in *M. leprae.*[40,42]

MECHANISMS OF IMMUNITY

Leprosy is not an easily transmitted infection. Many people may be resistant to infection by *M. leprae* even during heavy exposure. Other people may be infected with *M. leprae* but never develop clinical leprosy, suggesting that either the cell-mediated immune response has cleared the infection or the infection is controlled or becomes latent. People who do not have and will not develop leprosy may be positive on tests of granulomatous (Mitsuda lepromin skin test) or humoral (anti–PGL-1 serology) immune response to *M. leprae.* There is likely an innate immune response that protects these people from disease development.

The likely first interaction between *M. leprae* and the human immune system is with resident macrophages and dendritic cells in mucosal surfaces via pathogen recognition receptors. The impact of this interaction on proinflammatory or antiinflammatory cytokine release may be what determines the subsequent course of infection.[43] Toll-like receptors and nucleotide-binding oligomerization domain (NOD)–like receptors recognize *M. leprae* antigens and have been associated with the development of leprosy per se and paucibacillary versus multibacillary phenotypes in genetic studies.[22]

People with a strong cell-mediated immune response to *M. leprae* have localized infection with formation of granulomas, manifested as paucibacillary leprosy.[44] People without a strong cell-mediated response have more disseminated disease, higher bacterial load, antibodies to the organism, and, clinically, lepromatous leprosy. Transcriptome studies of leprosy skin lesions have confirmed distinct gene expression profiles in tuberculoid versus lepromatous leprosy lesions. Tuberculoid lesions have higher expression of genes associated with antigen processing and proinflammatory cytokines, while lepromatous lesions have higher expression of genes associated with antiinflammatory cytokines and B cells.[45] A recent systematic review on the role of human genetics in polarization to tuberculoid or lepromatous leprosy identified 28 genes with haplotypes or SNPs associated with paucibacillary versus multibacillary leprosy, including genes encoding pathogen recognition receptors.[22] Additional pathways associated with different clinical manifestations of leprosy are type I interferon-induced pathways inducing increased cell-mediated immune response[46] and inhibition of autophagy pathways leading to higher macrophage *M. leprae* burden in multibacillary leprosy.[47] Most immunologic studies in leprosy can describe the "how" of the immune status of people with different clinical forms of leprosy, but to date we do not understand the "why" of what causes a person to develop a strong cell-mediated versus strong humoral immune response to *M. leprae.*

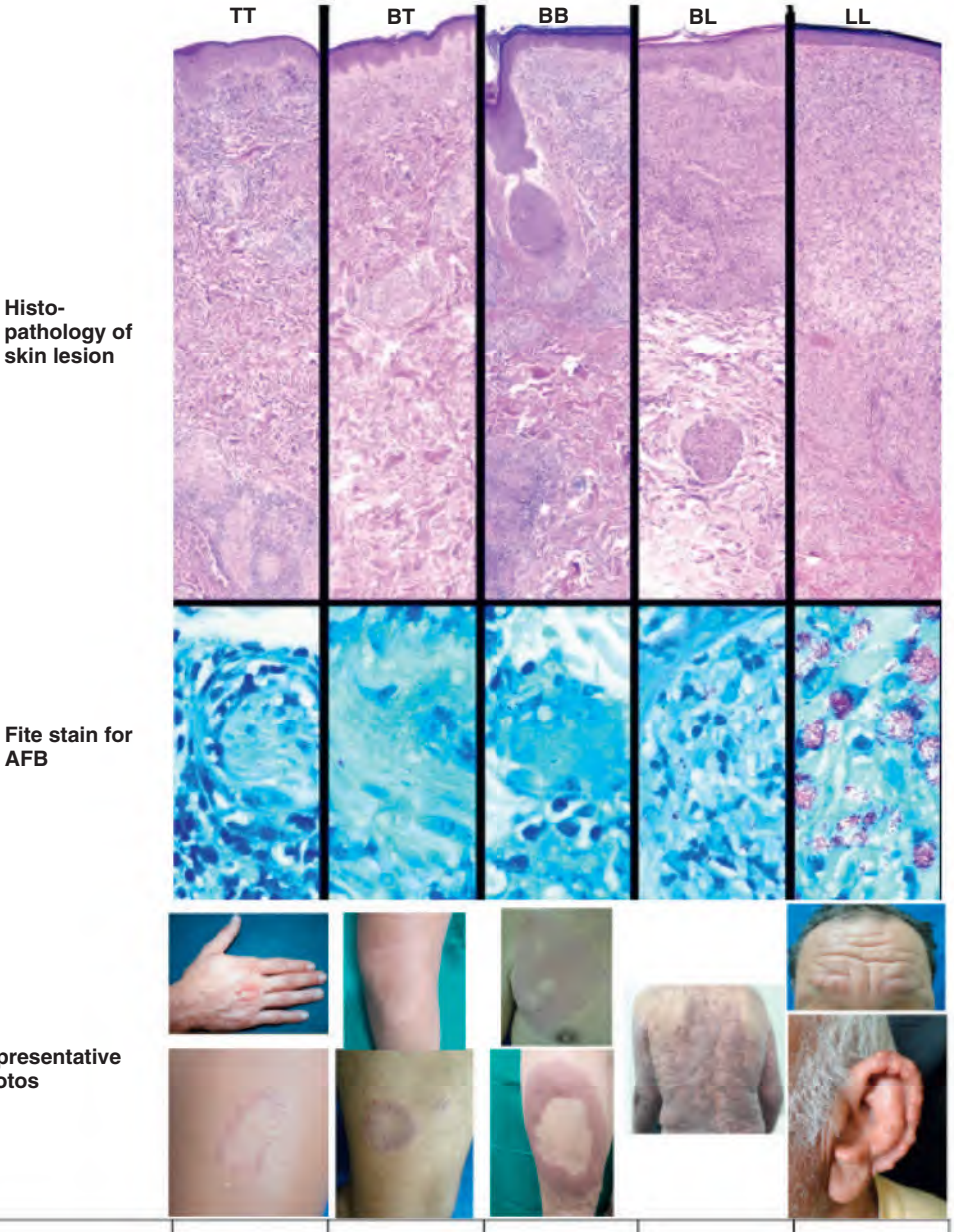
CLINICAL MANIFESTATIONS OF LEPROSY

> If immunology is the root of the tree, its fruit is the knowledge of infectivity, prognosis, and management of the patient.[48]

A wide variety of clinical presentations can result from *M. leprae* infection. In 1953, the "Madrid classification" was proposed, which included a tuberculoid form, a lepromatous form, and "dimorphous" leprosy that was intermediate between the tuberculoid and lepromatous forms. An "indeterminate" classification was also included, which is the initial lesion of leprosy; it theoretically can either heal or develop to a lepromatous or a tuberculoid form, depending on host immune response.[49] Dimorphous leprosy is considered a manifestation of immunologic instability, wherein leprosy will eventually transition to a more tuberculoid or more lepromatous form.

A more rigorous classification system incorporating clinical findings, histopathology, bacterial index, and immunologic parameters was proposed by Ridley and Jopling in 1962 (Fig. 250.3).[50] Recognizing that leprosy occurs on a continuous spectrum, it considers a person's "resistance" to *M. leprae* infection and subdivides leprosy into five types.[48] The Ridley-Jopling classification includes polar tuberculoid (TT) and polar lepromatous (LL), but subdivides dimorphous leprosy into three borderline types: borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL) (see Fig. 250.3). The tuberculoid pole is characterized by a strong cell-mediated immune response to *M. leprae,* with histopathology of skin biopsies showing well-formed granulomas and infiltration of nerves and few or no bacilli. The lepromatous pole is characterized by a poor cell-mediated immune response to *M. leprae,* and skin biopsies have foamy macrophages and large numbers of bacilli. The borderline forms are more unstable and have components of both cell-mediated and humoral immune responses to *M. leprae.*

The WHO developed a classification system for leprosy diagnosis and treatment recommendations that could be implemented in resource-limited settings. Presumptive diagnosis of leprosy is based on hypopigmented or reddish skin lesion with loss of sensation, peripheral nerve symptoms, or skin smear with AFB. The WHO schema contains two groups, paucibacillary and multibacillary leprosy, which determines length of recommended antibiotic regimen. If a person has five or fewer hypopigmented, hypoesthetic skin lesions, the designation is paucibacillary. If a person has more than five skin lesions, the designation is multibacillary, which necessitates a longer course of multiantibiotic treatment for leprosy[51] (Table 250.1). The Ridley-Jopling classification system provides additional information that can be helpful in determining appropriate treatment duration, risk for development of leprosy immune reactions, and monitoring response to treatment and should be utilized when possible.



	TT	BT	BB	BL	LL
Types of lesions	macule plaque raised border annular	macule plaque raised border satellite lesions	macules plaques "targetoid"	macules papules plaques nodules asymmetric	macules plaques nodules diffuse symmetric
Sensation in lesions	markedly diminished or absent		slightly to moderately diminished		slightly diminished or normal
Nerve enlargement	asymmetrical single or few nerves		more likely to be symmetrical several nerves		"stocking and glove" anesthesia possible
Risk for immune reactions	very rarely RR	RR	RR	RR ENL	ENL Lucio phenomenon

FIG. 250.3 Immunopathologic spectrum of leprosy, representing the five histopathologic subtypes of leprosy in the Ridley-Jopling classification. *Top,* Hematoxylin and eosin–stained sections (magnification ×63) showing well-formed epithelioid granulomas in TT progressing to disorganized histiocytes in LL. *Middle,* Fite-stained sections (magnification ×1000) showing scarce organisms in TT progressing to very high bacillary load in LL. *Bottom,* Representative photos are examples of clinical presentations for each of the Ridley-Jopling subtypes. *Table,* Characteristics of skin lesions and nerves on clinical examination and the risk for the pathologic immune reactions of leprosy. *AFB,* Acid-fast bacilli; *BB,* mid-borderline; *BL,* borderline lepromatous; *BT,* borderline tuberculoid; *ENL,* erythema nodosum leprosum; *LL,* polar lepromatous; *RR,* reversal reaction; *TT,* polar tuberculoid. *(Histopathology and Fite stain figures from Scollard DM, Adams LB, Gillis TP, et al. The continuing challenges of leprosy.* Clin Microbiol Rev. *2006;19:338–381; reprinted with permission. Clinical photographs courtesy Dr. Mauricio Nobre, Hospital Giselda Trigueiro, Natal, Rio Grande do Norte, Brazil.)*

TABLE 250.1 Recommended Regimens to Treat Leprosy in Adults

	WHO RECOMMENDATIONS[a]			US (NHDP) RECOMMENDATIONS[b]		
	Medication	**Dosage**	**Duration**	**Medication**	**Dosage**	**Duration**
Paucibacillary or "tuberculoid" leprosy (TT, BT, <5 lesions)	Dapsone Rifampicin Clofazimine Clofazimine	100 mg daily 600 mg once a month 50 mg daily 300 mg once a month	6 months 6 months 6 months 6 months	Dapsone Rifampicin	100 mg daily 600 mg daily	12 months 12 months
Multibacillary or "lepromatous" leprosy (BB, BL, LL, ≥5 lesions)	Dapsone Rifampicin Clofazimine Clofazimine	100 mg daily 600 mg once a month 50 mg daily 300 mg once a month	12 months 12 months 12 months 12 months	Dapsone Rifampicin Clofazimine	100 mg daily 600 mg daily 50 mg daily	24 months 24 months 24 months

[a]WHO treatment regimen guidelines from https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=1.
[b]US Department of Health and Human Services HRSA treatment regimen guidelines from https://www.hrsa.gov/hansens-disease/diagnosis/recommended-treatment.html.
BB, Mid-borderline; *BL,* borderline lepromatous; *BT,* borderline tuberculoid; *HRSA,* Health Resources & Services Administration; *LL,* lepromatous leprosy; *NHDP,* National Hansen's Disease Program; *TT,* tuberculoid; *WHO,* World Health Organization.

Indeterminate leprosy is the earliest visible manifestation of *M. leprae* infection. Indeterminate leprosy is a single macule that is usually hypopigmented, and may have slight decrease in sensation. There is generally still hair in the area of the lesion, but it may be drier than the surrounding skin. Biopsy of the lesion can be nonspecific, although perineural cuffing is typical of indeterminate leprosy. There may or may not be bacilli present in the lesion. The immune response to *M. leprae* has not been fully developed in people with indeterminate leprosy, and a person may self-resolve, progress to tuberculoid leprosy, or progress to lepromatous leprosy.

CLINICAL PRESENTATION

People with leprosy may present for medical evaluation with a wide variety of symptoms, related to the type of leprosy. During the initial assessment, a thorough travel and social history is essential. Risk factors for leprosy in the United States include history of residence in a country with a high burden of leprosy or in a state in which zoonotic transmission of leprosy is documented. Family history of leprosy is important both as a potential source of *M. leprae* infection and as an indicator of underlying genetic risk factors. On physical examination, a full skin survey should be completed to assess macules, papules, plaques, subcutaneous nodules, and infiltrative skin changes. Leprosy skin lesions are uncommon on the perineum and scalp and in the axillae, but otherwise can develop anywhere. Since the lesions themselves are asymptomatic, a person may not report lesions when they are in a nonvisible area of the body. Peripheral nerves should be assessed for enlargement and tenderness to palpation (Fig. 250.4). Symptoms such as numbness, tingling, weakness, and shooting pains should be specifically assessed for. Sensation should be tested in the hands and feet to detect subclinical neurologic involvement, which could necessitate additional treatments or interventions.

Skin lesions are a prominent feature of leprosy and can be macules, patches, papules, or nodules. Lesions may be reddish or hypopigmented. The earliest sensory change in leprosy skin lesions is compromised perception of the difference between warm and cold temperatures.[52,53] Affected skin may lack or have decreased hairs. Decreased sweating is related to autonomic cutaneous nerve compromise, but is more difficult to detect on clinical examination. Nerve dysfunction is most severe in people with strong cell-mediated immune response to *M. leprae.* People with leprosy may or may not have neurologic symptoms or subjective complaints at initial presentation. However, reduction or absence of sensation in a skin lesion is a very useful indicator to distinguish leprosy from other similar-appearing skin lesions.

Severe loss of sensation can lead to trauma and an initial presentation with burns, contusions, and lacerations, often in the region of skin lesions and without the expected associated pain. These are particularly common in the hands and feet, and can be associated with activities of daily living such as cooking, farming, or even holding a hot beverage. In extreme circumstances, people may present with acute or chronic localized muscle weakness, or even paralysis of an extremity. A hand in a claw position or a foot that drags on the ground while walking are strongly suggestive of leprosy, and warrant skin survey and investigation for other signs and symptoms suggestive of leprosy and leprosy immune reactions.

Skin lesions of lepromatous leprosy or diffuse leprosy are more subtle. The lack of cell-mediated immunity means that destruction of cutaneous nerves, hair follicles, and melanocytes are not prominent features, which changes the clinical presentation. Rather than discrete lesions, some people with polar lepromatous leprosy have infiltrative skin changes including loss of normal skin contours and skin thickening. One place to assess for this change is in the forehead. In advanced disease, a person may have loss of lateral eyebrows (superciliary madarosis) or eyelashes (ciliary madarosis) or both. There may be deformities of the nose (so-called saddle nose) or perforation of the nasal septum. Symmetrical enlargement and nodularity of the ears is also a classic finding for lepromatous leprosy. Diffuse involvement of the face in lepromatous leprosy results in infiltration and subcutaneous nodules (lepromas) with abundant *M. leprae.* Leprosy is in the differential diagnosis for "leonine facies."

The pathologic immune reactions of leprosy, reversal reaction and erythema nodosum leprosum (ENL), are significant contributors to morbidity related to leprosy. They may occur prior to, during, or after antibiotic therapy for *M. leprae* and are an indication for urgent evaluation and initiation of appropriate treatment. These reactions are discussed in following sections.

Infection of the eye by *M. leprae* and the impact of *M. leprae*–associated inflammation of muscles and nerves cause significant morbidity in leprosy. Direct damage can occur from chronic *M. leprae* infection per se, because *M. leprae* can enter the eye during initial dissemination of the infection. In lepromatous leprosy, there can be lepromas in the eyebrows and upper eyelids. In the eye, the cornea may have visible discrete particles and there may be white microlepromata on the surface of the iris. These are signs of chronic *M. leprae* infection with a high bacterial load. Additionally, both reversal reaction and ENL immune reactions can cause acute, serious ocular damage. In reversal reaction, nerve damage of the trigeminal nerve or facial nerve can cause lagophthalmos and defective blink reflex. The sequelae include permanent lagophthalmos, keratitis, corneal opacities, ectropion, entropion, and trichiasis. ENL's ocular manifestations include episcleritis, scleritis, and iridocyclitis. In cases of chronic inflammation in the eye, uveitis can cause nerve damage that leads to iris atrophy, more than one pupil, and low intraocular pressure.[54] Ocular complications can occur even after multidrug therapy is completed.[55] An additional consideration in people with leprosy and immune reaction on long-term steroids is the increased risk for developing steroid-related cataracts.

There is a specific type of leprosy called diffuse lepromatous leprosy, or Latapí lepromatosis. This form of leprosy is most common in Mexico, and may be associated with either *M. leprae* or *M. lepromatosis* infection. In a study of 300 cases of diffuse leprosy in Mexico diagnosed between 1970 and 2004, 90.5% were from the Pacific Coast states of Mexico.[56] People with diffuse lepromatous leprosy are at risk for necrotic vasculopathy,

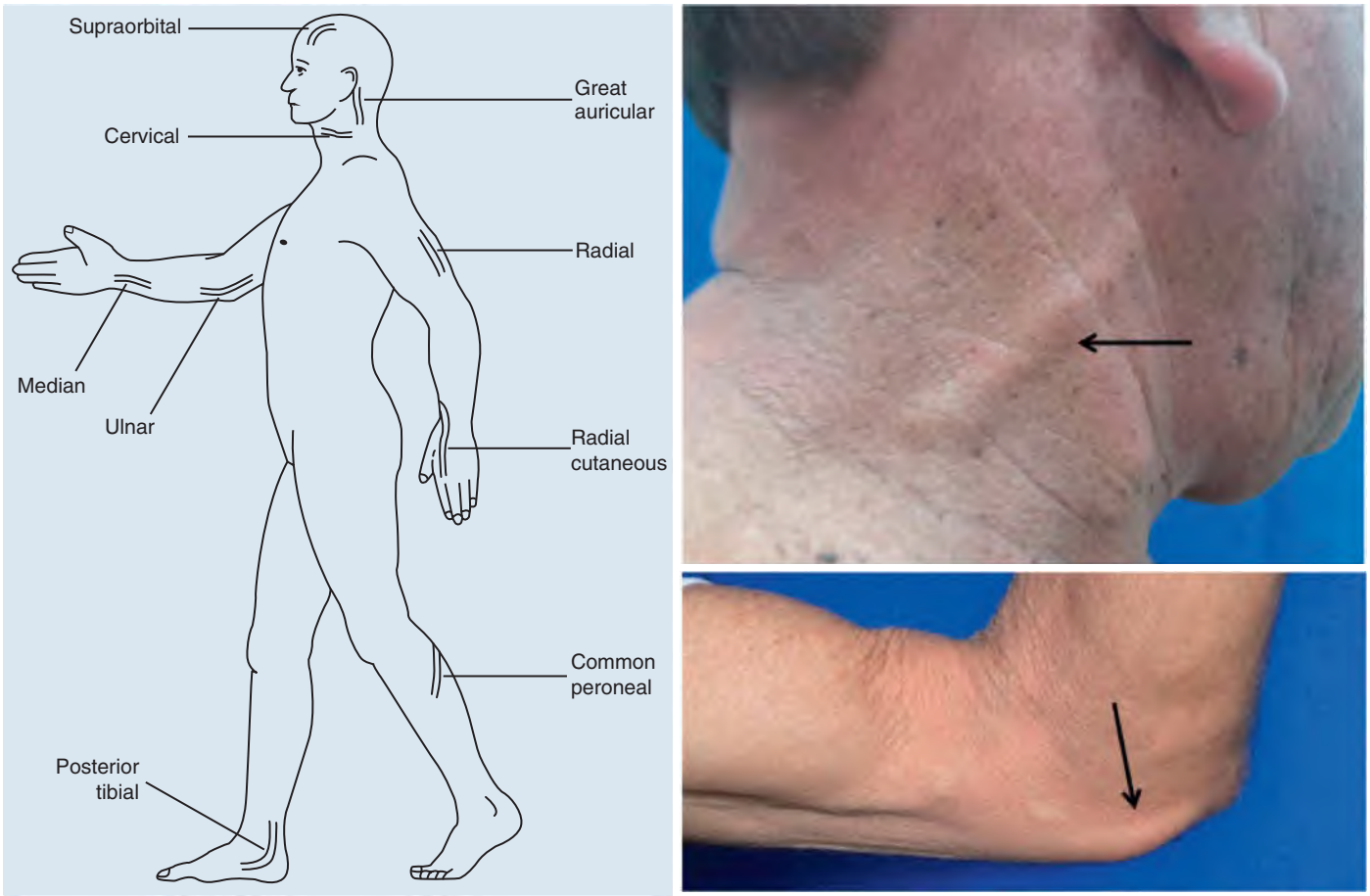


FIG. 250.4 Palpation of peripheral nerves to assess size, nodularity, and tenderness. Palpation of peripheral nerves is a key component of the physical examination of a person suspected of having leprosy. *Left,* Map of the palpable nerves that can be affected during leprosy. *Top right,* Enlarged right auricular nerve *(arrow). Bottom right,* Enlarged left ulnar nerve *(arrow)* in a patient with reversal reaction and neuritis. *(Left image from Hastings RC.* Leprosy. *2nd ed. New York: Churchill Livingstone; 1994, reprinted with permission. Right images courtesy Dr. Mauricio Lisboa Nobre, Hospital Giselda Trigueiro, Natal, Rio Grande do Norte, Brazil.)*

referred to as Lucio phenomenon. This vasculopathy can progress to multiple cutaneous infarcts that may be fatal, so early recognition of this form of leprosy can be lifesaving.[38] The skin lesions of diffuse lepromatous leprosy are much less prominent. The infiltration of *M. leprae* is so diffuse that in the early stages the skin appears smooth and shiny. After subcutaneous tissue has been destroyed by infection, the skin is looser and wrinkled. Nodules, if present, are palpable subcutaneously but generally not visible as in lepromatous leprosy or ENL. One retrospective study of diffuse lepromatous leprosy treated in California over a period of 35 years found that the median delay in diagnosis was 3 years, and in many people the diagnosis was only reached when they presented with necrotic vasculitis.[57] This delay in diagnosis was also reported in the aforementioned study from Mexico, where the time from appearance of first sign of leprosy and the diagnosis of leprosy varied from 1 week to 12 years, with a median of 3 years.[56] Prompt treatment of the underlying mycobacterial infection in diffuse lepromatous leprosy can prevent this complication. Associated findings are madarosis and chronic rhinitis, which can be the presenting complaints of diffuse lepromatous leprosy. With the appropriate history, leprosy should be included in the differential diagnosis.

Prominent pathologic features of diffuse leprosy are in the cutaneous vasculature, with AFB visible in endothelial cells and fibrin clots in blood vessels. In early stages, the vessel lumen can decrease because of intimal thickening. As the infection progresses, AFB are visible in more blood vessels and the vessel lumen size decreases further. Eventually the vessel lumen is no longer visible and there may be foamy macrophages around the blood vessels. When ischemic necrosis develops, the epidermis and superficial dermis develop necrosis and vascular occlusion caused by thrombus or intimal thickening. There may be fibrin deposition and an inflammatory infiltrate with many types of immune cells.[56]

Primary neural leprosy is another diagnostic challenge in leprosy.[58] In this form of leprosy, the presentation can be of nerve pain, paresthesias, weakness, or paralysis. On examination, there is a lack of leprosy skin lesions. The affected nerve is generally enlarged and tender to palpation, with palpation eliciting both localized pain and shocklike pain that radiates in the distribution of the nerve. Additional findings can include muscle weakness, atrophy in the muscles innervated by the affected nerve, decrease in sensation in the area of innervation, or paralysis. People may present with acute neuritis, and should be considered for acute initiation of corticosteroids to decrease nerve swelling and associated neurologic compromise. Primary neural leprosy can affect one or multiple nerves, and treatment duration is generally a reflection of the number of nerves involved—paucibacillary course for single nerve and multibacillary course for multiple nerves. Nerve biopsy can assist in diagnosis by demonstrating AFB and inflammatory changes, although visualization of AFB is not required for a diagnosis of neural leprosy. However, there are risks of nerve damage with nerve biopsy. Electromyography of affected nerve(s) can be consistent with demyelinating mononeuropathy.[58–60]

DIAGNOSTIC TESTING

Histopathology of skin biopsy is most helpful for confirming a diagnosis of leprosy and to determine the Ridley-Jopling clinical form. It is very important to select an appropriate lesion and to biopsy in the appropriate area. Generally, the most active margin of the most active

lesion should be biopsied at the edge of the lesion. In most lesions, the infection is most pronounced at the border. This is especially important for targetoid lesions since the central area will have different pathologic findings and bacillary loads from those of the border. Skin biopsies can be of the "punch" variety, optimally full thickness and including the deep dermis. The pathologist should be advised as to the clinician's suspicion for leprosy, with a special request for acid-fast staining, in particular the Fite stain, which is the stain of choice for detecting *M. leprae.* The Fite staining methodology includes oil in the deparaffinizing reagent to help maintain the integrity of the *M. leprae* cell wall such that it remains acid fast during the staining procedure, thus increasing the sensitivity of the stain. Standard Ziehl-Neelsen stains may be negative for AFB, even when AFB are seen with the Fite stain.[61] Additionally, standard hematoxylin and eosin staining is crucial for histopathologic characterization of the type of immune infiltrate and involvement of cutaneous nerves. It is important to note that a leprosy lesion may be negative for AFB. This is particularly true in the polar tuberculoid and borderline tuberculoid forms of the disease. In these cases there are classic histopathologic signs of leprosy, including perineural inflammation, which are nearly pathognomonic for the diagnosis.

Histopathologic findings of leprosy can be focal and variable in a single biopsy. In paucibacillary leprosy, there may be very small numbers of or no *M. leprae* visible in polar tuberculoid disease. Typical pathologic findings are presented in the earlier section on "Clinical Manifestations of Leprosy" and in Fig. 250.3. The Fite staining method is not specific for *M. leprae,* and confirmation of *M. leprae* requires a molecular diagnosis. At the time of this writing, biopsies containing AFB on staining with negative mycobacterial cultures can be reviewed by the NHDP. All biopsies reviewed by NHDP are tested for *M. leprae* by polymerase chain reaction (https://www.hrsa.gov/hansens-disease/diagnosis/biopsy.html). *M. leprae* can be detected in areas other than the skin and nerves, but this is not sensitive for leprosy. If *M. leprae* were present, it would be only in cases of lepromatous leprosy.[62] Even if present, *M. leprae* in tissues can reflect sporadic, transient dissemination of *M. leprae* or organ involvement.

Slit-skin smear testing is one method to confirm that leprosy is multibacillary. For accurate and precise results, smear collection and interpretation of the stained material should be completed by trained personnel.[63,64] The NHDP recommends diagnostic skin smear from 6 sites: bilateral earlobes, elbows, and knees, and from the margin of one or more skin lesions. The NHDP has a protocol for collection of the skin smears (https://www.hrsa.gov/hansens-disease/diagnosis/skin-smears.html). Briefly, a 3- to 5-mm long incision is made 2 to 3 mm deep to the skin surface. Pressure is maintained internal to the incision to decrease vascularity temporarily. The blade is used to scrape the incision, which collects dermal tissue and fluid. This material is placed on a slide and dried at room temperature for later Fite acid-fast staining. The NHDP can perform Fite staining and determination of the bacterial index, at no cost to the patient. The bacterial index is determined by counting the number of bacilli per oil immersion field. The *M. leprae* bacterial index is on a semi-logarithmic scale from +1 (1–10 bacilli per 100 fields) to +6 (over 1000 bacilli per field). This method detects both viable and nonviable bacteria. Clearance of *M. leprae* by immune cells is a very slow process. On serial slit-skin smear tests, the bacterial index will decrease an average of 1 point per year. Consecutive monitoring of bacterial index can be helpful to document response to antibiotic treatment. A consistently increasing bacterial index can be a sign that bacteria is resistant to the antibiotics, the infection has recurred, or that a cured patient has been reinfected.

When a skin lesion is consistent with leprosy, but sensation testing does not reveal a definitive deficit in touch or temperature sensation, one option to assist with diagnosis is to assess response to histamine.[65] Histamine skin prick tests are used as a positive control for allergy skin testing panels. In normal skin, histamine introduction results in a "triple response" of (1) local redness, followed by (2) a more disseminated flare, and (3) the wheal. Since the flare results from reflex dilation of arterioles, leprosy lesions do not have a flare because *M. leprae* infection and immune response to it have compromised the sensory nerves that generate the flare response. An "incomplete" histamine response, in which the flare is absent in the area of the lesion but present in unaffected skin, is specific for leprosy.[66]

The lepromin or Mitsuda skin test is an assessment for granulomatous response to *M. leprae* antigen.[67] Killed *M. leprae* is injected subcutaneously, and assessed after 4 weeks for development of palpable induration at the site of injection, and for granuloma formation on biopsy. The lepromin skin test is of limited utility as part of a diagnostic workup. It is not available in the United States and is not US Food and Drug Administration (FDA) approved. It is not in widespread use worldwide.

Serologic tests for leprosy are in development, including as a potential diagnostic or community screening tool for leprosy. The most studied serologic target is PGL, found in the cell wall of *M. leprae,* reviewed by Penna and colleagues.[68] A positive anti–PGL-1 serology can be found in people with lepromatous forms of leprosy and high antibody levels. However, healthy community controls can also have positive PGL-1 serologies, which may be related to prior exposure or subclinical infection, or may be a false positive. In addition, results are negative in most tuberculoid (TT and BT) patients, which means that the test misses a large percentage of cases of leprosy. A recently developed serologic assay of antibody response to a multiantigen fusion protein, termed Leprosy IDRI Diagnostic (LID)-1, is in use in Brazil and is available for research purposes only in the United States. However, the sensitivity and specificity of this test in leprosy per se precludes its use as a stand-alone diagnostic tool.

TREATMENT OF LEPROSY

Antibiotics

Leprosy is curable with multidrug antibiotic therapy. This has been the standard of care in the United States since 1981 and worldwide since 1982. At the time of this writing, multidrug therapy is available for free to any patient diagnosed with leprosy, either through the WHO or from the NHDP for people in the United States. Multidrug therapy has dramatically improved prognosis for people diagnosed with leprosy, and has resulted in significant decline in the rates of leprosy worldwide.[69] The current dosing regimens recommended by the WHO and NHDP are shown in Table 250.1. "Uniform multidrug therapy" in which paucibacillary and multibacillary leprosy are both treated with a three-drug, 6-month regimen, has been evaluated, although at this time it is not part of national or global recommendations.[70–72]

The antibiotics routinely used in leprosy multidrug therapy are dapsone, rifampin, and clofazimine. In leprosy treatment programs that use WHO-distributed blister packs, multidrug therapy for leprosy is often administered as modified directly observed therapy, where medications are dispensed once a month. At this time, a monthly dose supplemented with rifampin and a higher-dose clofazimine is administered under supervision. For people who are unable or unwilling to take certain components of the standard multidrug therapy regimen, there are alternative antibiotics that can be substituted for individual components of multidrug therapy. These include clarithromycin, ofloxacin, and minocycline.[51,73]

The first antibiotic found to be effective for leprosy was dapsone in the 1940s.[74] Dapsone monotherapy is no longer appropriate given the development of resistance when dapsone is used as a single agent, but it remains a key component of multidrug therapy. People with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at risk for dapsone-induced methemoglobinemia, so screening for G6PD deficiency before starting dapsone is recommended unless in a resource-limited setting where G6PD testing is not available. Anemia is a common side effect of dapsone, even in people without G6PD deficiency, and is a sign that alternative multidrug therapy regimens should be considered.[75] Severe side effects include potentially fatal blood dyscrasias such as agranulocytosis and aplastic anemia and dapsone hypersensitivity syndrome. The hypersensitivity syndrome is characterized by exfoliative dermatitis, lymphadenopathy, fever, and hepatosplenomegaly and has a mortality rate of almost 10%. A genome-wide association study of dapsone hypersensitivity syndrome in leprosy in China found an association with HLA-B*13:01 haplotype.[76]

Rifampin is the most bactericidal agent in the multidrug therapy regimen. In mouse studies, a single dose of a rifampin-containing

multidrug regimen decreased viable *M. leprae* almost to the limit of detection as determined by inoculation of a normal mouse footpad.[32] Rifampin is included in both paucibacillary and multibacillary treatment regimens with monthly (WHO guideline) or daily (NHDP guideline) dosing. Rifampin should not be used as monotherapy, because of the risk of development of resistance. Rifampin induces multiple components of the cytochrome P-450 system, resulting in significant drug interactions, including with oral contraceptives and corticosteroids. Use of a drug interactions database at initiation of multidrug therapy and with any changes in regimen are recommended to decrease likelihood of adverse reactions related to interactions. Rifampin can cause orange discoloration of bodily fluids, hepatotoxicity, and hypersensitivity reactions, including DRESS (*d*rug *r*eaction with *e*osinophilia and *s*ystemic *s*ymptoms) syndrome. People taking rifampin may also report a flulike syndrome, which may be related to intermittent dosing or dosage, or both.[77]

Clofazimine is a bacteriostatic antibiotic that also has antiinflammatory activity. It is used in the treatment of multibacillary leprosy, and also for treatment of ENL at higher doses. Clofazimine was FDA approved in 1986, but is no longer commercially available. Clofazimine is obtainable in the United States from the NHDP as part of an investigational new drug application from the FDA for leprosy treatment. Clofazimine is generally well tolerated at the doses used to treat leprosy. It is lipophilic, and a major side effect is hyperpigmentation from deposition of clofazimine in the skin, particularly in areas of inflammation. The hyperpigmentation is worsened with sun exposure, in addition to other symptoms of clofazimine-associated photosensitivity. The hyperpigmentation is not harmful and resolves after stopping clofazimine, but the symptom can be very distressing to the patient. Often this is because the pattern of hyperpigmentation is recognized in a person's community as a sign of leprosy. There have been reports of depression and suicide in people taking clofazimine, thought to be related to distress about the skin changes.[78] Uncommonly, and especially when used at higher doses than those used in standard multidrug therapy, clofazimine can cause abdominal discomfort and enteropathy related to clofazimine crystal deposition.[79] Alternatives to clofazimine are detailed in leprosy treatment recommendations.[51,73,80]

Drug Resistance

Resistance of *M. leprae* to multidrug therapy is thought to be uncommon. Resistance testing is generally done as part of national and global surveillance to assess continued efficacy of multidrug therapy for leprosy on a population level,[81] and is not currently the standard of care for individual patients. Gold standard resistance testing requires successful inoculation and propagation of *M. leprae* in the mouse footpad, which is not feasible in most cases. Molecular methods can also be used to deduce drug resistance from mutations in *folP1* (dapsone), *rpoB* (rifampin), and *gyrA* (ofloxacin). Even with molecular testing, there needs to be enough bacteria in the specimen for DNA isolation, amplification, and sequencing, which limits its use in tuberculoid leprosy. In the United States, molecular testing for mutations associated with resistance to dapsone, rifampin, and quinolones may be available through the NHDP.

Surgical Intervention

There are some situations in acute and chronic management of leprosy when surgical intervention may be indicated, including neuritis with neurologic compromise that has not improved with steroids. The first-line therapy for acute neuritis and nerve function impairment is high-dose corticosteroids. If, despite this intervention, the nerve remains compressed, the resulting neurologic deficit(s) can be permanent. In these and some other special cases, surgical decompression of the nerve can be considered to maximize return of function and for pain control.[82,83] A Cochrane review of decompressive surgery for nerve damage in leprosy determined that the randomized control trials published up to 2012 were not of high enough quality to assess effectiveness of this intervention for ulnar neuropathy.[84] People with footdrop from posterior tibial nerve involvement and decreased sensation in the sole of the foot are at increased risk for foot ulcers related to altered gate and increased pressure on the forefoot. Tibialis posterior transfer surgery can improve gait and weight-bearing distribution to decrease risk of foot injury and deformity.[85]

Laryngeal involvement by *M. leprae* can cause dysphonia, stridor, and in rare cases airway obstruction.[86] Airway obstruction from laryngeal leprosy requiring emergency tracheostomy has been reported.[87] Fortunately, this complication has become very rare in an era of curative multidrug therapy for *M. leprae*.

After leprosy cure, reconstructive surgery may be desired by a patient to reverse physical changes that occurred due to the infection. These may include surgical intervention for lagophthalmos, reconstruction of nasal bridge in saddle nose deformity, release of contractures, or resection of hypertrophied earlobes. The role of surgery for complications of leprosy has been reviewed by Virmond and coworkers.[88]

Physical Therapy and Occupational Therapy Interventions

At the time of diagnosis of leprosy, a person should have a full sensory, motor, and neurologic function evaluation. This evaluation should be repeated at the termination of leprosy treatment, in the case of reactions, or for changes in a patient's signs or symptoms. The neurologic changes from leprosy may be visible or silent.[89] If any compromise is noted, evaluations by a physical therapist and an occupational therapist are indicated, with practitioners experienced in peripheral neuropathies if available. Guidance for self-care should include (1) inspection for skin factors that predispose to wounds, (2) knowledge about potentially dangerous activities, (3) prevention such as using protective footwear, and (4) basic wound management.[90] The Innovative Care for Chronic Conditions model has been applied to self-care programs in leprosy, where physicians and health care professionals are advised to "help people to create plans that will help them achieve their goals."[91]

The International Federation of Anti-Leprosy Associations (ILEP) has published a series of learning guides (https://www.leprosy-information.org) that can be helpful in orienting the medical team and patient to self-care activities to prevent disability.[92] The sequelae of leprosy are chronic, and the interventions to improve functioning and decrease development of additional morbidity from trauma and infections related to sensory and autonomic damage in the extremities often need to be lifelong. People with disability at diagnosis, with neuritis, and with more disseminated disease have increased risk for developing additional disability in the years following leprosy cure,[93] and may benefit from more frequent follow-up or reinforcement of self-care principles. The NHDP has developed a multidisciplinary program to decrease lower extremity amputations in people with decreased protective sensation in the feet, called Lower Extremity Amputation Prevention (LEAP). LEAP includes (1) annual foot screenings to identify sensation changes, (2) education, (3) daily self-inspection of feet, (4) appropriate footwear, and (5) prompt intervention for foot problems when they develop.[94]

Monitoring Treatment Response

Clinical response to treatment can be very slow. Patients may become discouraged when they do not see rapid improvement, so additional social support may be needed to maintain compliance with the regimen. Additionally, the development of reactions can be seen by care providers and patients as a worsening brought on by antibiotics, when in fact the reactions are merely a sign of reactivity to *M. leprae*. Notably, *M. leprae* are highly resistant to degradation in the tissues, even when no longer viable. Histologic demonstration of AFB in tissue sections is not necessarily evidence of active disease. Minimal reduction of the bacterial load may be seen in the first 2 years, even though multidrug therapy is highly effective in killing the bacilli. Fragmented and degenerating bacilli may be seen in Fite stains for several years after discontinuing multidrug therapy (Fig. 250.5).[35] Mouse studies have shown that these bacteria are not viable.[95]

There are some situations in which leprosy lesions can appear to worsen or there are new skin lesions during or after multidrug therapy. The most common cause of these worsened or new lesions is leprosy immune reactions. Although most common in the first months after starting multidrug therapy for leprosy, reversal reaction can develop at any time, including after multidrug therapy has been completed and *M. leprae* infection is cured. Immune reaction is much more common than relapse as the cause of worsening skin lesions in leprosy. When relapse occurs, it is generally in people who had a high bacterial load

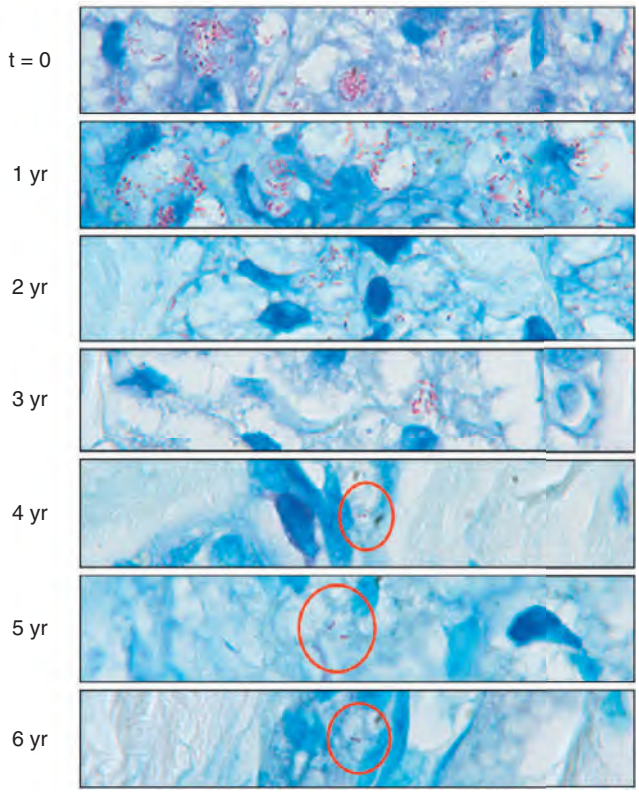


FIG. 250.5 Fite stains for *Mycobacterium leprae* remain positive for years after the bacteria are no longer infectious. These Fite stains (magnification ×1000) of biopsy material were obtained yearly from a person with lepromatous leprosy from the time of diagnosis (top panel: *t* = 0). At 1 year, the bacteria do not stain as solid, indicating that the bacteria have begun to degenerate. In subsequent years, the bacterial index continues to decrease as the bacteria degrade or are cleared by the immune system, or both. This patient was treated for 2 years with multidrug therapy according to the NHDP guidelines, and did not have a relapse. This figure illustrates that a biopsy may stain positive for bacteria for years after a person is no longer infectious and has been cured of the infection. *(From Scollard DM, Stryjewska B. Treatment and prevention of leprosy. In: von Reyn CF, ed. UpToDate:* Nontuberculous Mycobacterial Infections*; reprinted with permission. Last updated December 1, 2016.)*

at the time of starting multidrug therapy. This may be related to *M. leprae* in immunologically protected sites where antibiotics do not penetrate, such as the eye or testis. Relapse due to multidrug resistance is even more uncommon. This may be related to drug resistance of the initial infecting *M. leprae* strain, or to the emergence of drug resistance during multidrug therapy. Because drug resistance is so rare, the WHO recommendation is to re-treat *M. leprae* relapse with a standard multidrug therapy course.[80] Leprosy caused by reinfection with a new strain of *M. leprae* is rare, and may be related to a household contact with untreated multibacillary leprosy.[96]

PREVENTION OF LEPROSY

The current focus of leprosy prevention and control efforts is for early diagnosis of leprosy cases so that treatment can be initiated promptly. This has the dual benefit of decreasing leprosy-related disability for the patient, as well as decreasing the time that a person could potentially transmit *M. leprae.* There is currently no FDA-approved vaccine for leprosy. In India, a vaccine with *M. indicus pranii* is in use for prevention and as an immunotherapeutic.[97–99] An *M. leprae*–specific candidate vaccine (LEP-F1 + GLA-SE) is being evaluated in a phase I safety and immunogenicity trial as of this writing (NCT03302897 at https://clinicaltrials.gov).

It is recommended that household contacts of people with newly diagnosed leprosy be evaluated for symptoms and signs of leprosy on examination. Additionally, this interaction with the health care system provides opportunities for education about leprosy and symptoms for which medical advice should be sought. Additional interventions are used in some countries to decrease risk of developing leprosy in these contacts, as summarized by Gillini and colleagues.[100] One intervention that can provide partial protection is bacillus Calmette-Guérin (BCG) vaccination.[101] In a Brazilian study of over 5000 contacts of leprosy patients, BCG vaccination or revaccination at the time of identification as a leprosy contact gave 56% protection compared with contacts who did not receive BCG.[102] For multibacillary leprosy, protection with BCG vaccination reached 88%. One precaution to note with BCG vaccination is that in a recent field study, researchers found that 0.4% of contacts who received BCG vaccine presented with paucibacillary leprosy in the 12 weeks after vaccination.[103] Almost half of these early diagnoses postvaccination had neuritis or reversal reaction. It is unclear if BCG vaccination decreased the incubation period or changed the pathogenesis of *M. leprae* infection.

Postexposure prophylaxis of household contacts with single-dose rifampicin has been studied as an intervention to decrease leprosy in regions hyperendemic for leprosy. Concerns have been raised about potential induction of rifampicin resistance in *M. tuberculosis* from single-dose rifampicin, but emergence of rifampin-resistant *M. tuberculosis* in a community that has received rifampicin for leprosy postexposure prophylaxis has not been documented.[104] In French Polynesia, 2751 residents were treated with single-dose rifampicin. Comparing 10 years of posttreatment new leprosy case detection rates to those from the prior 20 years showed a 70% rate of protection.[105] In a double-blind, cluster-randomized, placebo-controlled study, 21,711 household and neighborhood contacts of 1037 people with leprosy in northwest Bangladesh received a single dose of rifampicin as postexposure prophylaxis.[106] Of note, only 28% of the leprosy index cases had multibacillary leprosy, which is the form of leprosy in which risk of transmission is highest. The reduction in incidence in the rifampicin prophylaxis group was 56.5% 2 years later, and 34.9% at 4 years. The number needed to treat to prevent one new case of leprosy at 4 years was 297. Efficacy of single-dose rifampicin was highest in contacts of paucibacillary leprosy, females, serology (anti–PGL-1) negative contacts, those with no history of BCG vaccine, and more distant contacts of the case.[106] Persons with the closest contact (e.g., immediate household members) had minimal benefit from single-dose rifampin. A secondary analysis, using a presumed BCG scar as a marker for perinatal BCG vaccination, found a combined 80% protection for single-dose rifampicin in people who had received perinatal BCG vaccination. The study protocol for a cluster-randomized controlled study (Netherlands clinical trial NTR3087) of single-dose rifampicin plus new or booster BCG immunization for postexposure prophylaxis for contacts has been published,[107] although results on efficacy are not available at the time of this writing.

PATHOLOGIC IMMUNE REACTIONS OF LEPROSY

Reactions are a significant cause of additional morbidity for people with leprosy.[108] Neurologic sequelae from immune reactions can be irreversible. Reactions can occur prior to, during, or after treatment for leprosy. Reactions are characterized as extension or worsening of skin lesions and symptoms due to immunologic responses to *M. leprae;* they are not drug reactions nor are they signs that *M. leprae* infection is worsening. For patients who are still on multidrug therapy, it is very important to continue the therapy for the full recommended course. Even when bacteriologic cure has been reached, reactions can persist. Reactions are often recurrent and can remit and recur for years, with long-term corticosteroids or other immunomodulatory medications required to control symptoms.

Type 1 Reversal Reaction

People with the unstable borderline forms of leprosy (BT, BB, and BL) are at risk for reversal reaction. This reaction is characterized by increased erythema and induration of preexisting lesions, and is the result of spontaneous enhancement of cell-mediated immunity in these lesions (Fig. 250.6). The most serious manifestation of reversal reaction is neuritis with sudden loss of nerve function. There is a validated severity scale for reversal reaction, but the components that comprise the scale require

FIG. 250.6 Reversal reactions are characterized by erythema and edema of existing leprosy skin lesions and appearance of new lesions. Reversal reactions may also be associated with neuritis. *(Courtesy Dr. Mauricio Lisboa Nobre, Hospital Giselda Trigueiro, Natal, Rio Grande do Norte, Brazil.)*

evaluation by proficient practitioners.[109] The scale includes cutaneous signs of reversal reaction, voluntary muscle testing, and muscle power.

Neuritis during reversal reaction can present as facial palsy, ulnar nerve palsy resulting in inability to extend at the wrist, and peroneal nerve palsy with inability to flex at the ankle (footdrop). Patients will generally report shooting, shocklike pains in the distribution of the nerve. These pains can be reproduced by palpation on examination. Affected nerves will commonly be enlarged relative to the contralateral nerve (see Fig. 250.4). Acute neuritis with loss of function needs to be treated emergently with corticosteroids. With prompt initiation of corticosteroids and resultant decrease in nerve swelling within the nerve sheath, function can return. Recommended starting dose is prednisone 1 mg/kg with slow taper off when symptoms have improved.[110] In a small case-control study with 21 people, comparing prednisone at 2 mg/kg with 1 mg/kg starting dose for ulnar neuropathy, the higher dose resulted in faster results in the first month, but both dosing regimens were ultimately equally effective.[111] A fixed dosing schedule for reactions has been recommended by the WHO. A study comparing a fixed prednisolone treatment schedule of 20 weeks with a longer treatment of 32 weeks did not show additional improvement in nerve function impairment with the longer duration of prednisolone. The authors recommended a 20-week course of prednisolone with additional prednisolone in those patients for whom it is indicated.[112] When close monitoring by a specialist is possible, tailoring of corticosteroid dosing to symptoms and with consideration for steroid side effects is preferred.[113] Blood glucose and blood pressure monitoring should be continued during steroid treatment. In regions endemic for *Strongyloides,* treatment for *Strongyloides* should be considered prior to starting high-dose steroids.[114] Cases of fatal *Strongyloides* hyperinfection in people receiving corticosteroids for leprosy reactions have been reported.[115]

In addition to initiation of corticosteroids, the inflamed nerve should be immobilized, such as with a sling in the case of ulnar neuritis, to decrease irritation of the nerve and minimize further swelling. Patterns of sensory loss, in addition to range of motion and strength, should be monitored during steroid treatment and the evolution of the immunologic reaction. For reversal reactions that do not improve as expected with high-dose corticosteroids, treatment of concurrent infections may decrease systemic inflammation and lessen the severity of the reaction.[115a]

It is important to note that many studies that do not show benefit of corticosteroids in improving sensory or nerve function are conducted in people who have only mild nerve impairment or whose nerve impairment is chronic. Acute neuritis and neuritis during reversal reaction are different entities that are definite indications for corticosteroids. A Cochrane review on steroid use in leprosy addresses these issues.[116] Alternative immunomodulatory medications have been tested for their impact on improvement of nerve function impairment. In a randomized controlled trial of people with reversal reaction with acute neuritis, reactional skin lesions, or both who received prednisolone and placebo versus prednisolone and azathioprine for 24, 36, or 48 weeks, adding azathioprine to prednisolone did not improve outcomes.[117]

At this time there are no predictive biomarkers for risk of developing reversal reaction. Low-dose prophylactic prednisone (20 mg/day) for 4 months from the time of diagnosis in people with borderline leprosy was not effective at reducing development of nerve impairment or immune reactions at 1 year after starting multidrug therapy for leprosy.[118]

Neuritis

Neuritis can occur as part of reversal reaction or ENL, or independently. People with acute neuritis usually present with shooting pains in the distribution of the affected nerve as a chief complaint. Pain may be aggravated by movement or by certain actions. Nerves may be enlarged (compared to contralateral nerve) or nodular on physical examination, and tenderness to palpation can be exquisite (see Fig. 250.4). Prednisone should be started at 1 mg/kg/day as for reversal reaction.[110] Immobilization, as with a sling, can provide symptomatic comfort and decrease irritating movement. Minimizing movement during acute neuritis will decrease further inflammation and swelling of the nerve. There should be a full assessment for nerve function impairment, including both sensory and motor deficiencies, with comparison to baseline assessments. Patients should be followed with monitoring for symptom improvement and improvement in objective measures of nerve function.

Type 2 Erythema Nodosum Leprosum

ENL occurs in people with polar lepromatous or borderline lepromatous leprosy. The exact etiology of ENL is unknown; immune complex formation has been associated with ENL, although its role in pathogenesis is unclear.[119] People with ENL generally present with systemic symptoms including fever and malaise, which distinguishes ENL from reversal reaction, which is not associated with fever. ENL is characterized by tender, indurated nodules that number from a few to hundreds (Fig. 250.7). During ENL, there can be end-organ effects, presumably due to the immune reaction occurring at areas of mycobacterial deposition in internal organs. These can include the liver, kidneys, spleen, (rarely) adrenal glands, and testes. Episcleritis, scleritis, and uveitis can occur as part of ENL, which merits an emergency consultation with an ophthalmologist, in addition to corticosteroids and treatment for ENL.[54] Neuritis with nerve function impairment can be part of ENL,

FIG. 250.7 Erythema nodosum leprosum is characterized by tender, erythematous nodules that can become confluent. *(Courtesy Dr. Barbara Stryjewska, National Hansen's Disease Program, Baton Rouge, LA.)*

either as a neuritis or from ENL within the nerve itself. If the ENL includes a component of neuritis, corticosteroids are indicated to decrease perineural swelling and nerve compression. There is a validated clinical severity scale for ENL, in use primarily in research settings, which includes fever, characteristics of the skin lesions, joint inflammation, and pain.[120]

Treatment of ENL varies depending on the severity of the ENL and what medications are available in a particular country.[121] Thalidomide is an antiangiogenic agent with anti-TNF properties that causes severe birth defects, including phocomelia. However, thalidomide can dramatically improve ENL's systemic symptoms and lesions within 1 to 3 days. A study comparing thalidomide 300 mg daily and prednisolone 40 mg daily for moderate and severe ENL found that the mean time to resolution of cutaneous lesions was 10 days shorter in the thalidomide group and mean remission period was 5 times as long (10.9 vs. 2.2 months).[122] A slowed taper of thalidomide results in less reemergence of ENL.[123] However, thalidomide has proven teratogenic effects and cannot be used in anyone who is pregnant or who could become pregnant. Men taking thalidomide must use barrier protection during any sexual contact with women of childbearing potential, and should not donate sperm.[124] In some countries, thalidomide is prohibited because it is teratogenic. Because of the teratogenic effects, the WHO does not recommend use of thalidomide in ENL. When thalidomide is available, prescription by a physician, dispensing by a pharmacist, and dosing by the patient are tightly regulated.[125] Counseling and consent regarding thalidomide need to include risks of inadvertent or intentional diversion.[126] Additional side effects of thalidomide include drowsiness, constipation, and peripheral neuropathy.[124]

Another significant caution with using thalidomide for ENL is the risk of deep vein thrombosis (DVT). The risk of thrombosis is highest when thalidomide is coadministered with corticosteroids, and is most often seen during ENL treatment when thalidomide and prednisone are being cross-tapered.[127–129] In a 2012 review of the literature that included five cases of leprosy treated with thalidomide and prednisone, the mean time to DVT was 6 weeks (range, 2–10 weeks) after starting thalidomide.[129] In people with multiple myeloma receiving thalidomide and low-dose dexamethasone, the addition of a thromboprophylactic agent can decrease rates of venous thrombosis.[130,131] The impact of thromboprophylaxis on thromboembolism risk in people with ENL on thalidomide and prednisone is not known.

Non-thalidomide treatments for ENL include pentoxifylline, corticosteroids, and high-dose clofazimine.[121,132] Pentoxifylline reduces blood viscosity and inhibits the synthesis of TNF. A double-blind trial

FIG. 250.8 Lucio phenomenon is recognized clinically by erosions and ulcerations secondary to vasculitis.

on the efficacy of pentoxifylline and thalidomide for ENL found that thalidomide was superior, with only 5% of people on thalidomide still having skin lesions at 7 days, compared with 41% of people on pentoxifylline. Pentoxifylline can be considered for people who have contraindications to thalidomide.[133] In a pilot study of ENL in Ethiopia, 33 people were randomized to prednisolone plus cyclosporine or prednisolone alone. The prednisolone dosing and taper were different for the two groups. People with chronic ENL on cyclosporine and prednisolone had twice as many severe flare-ups as the prednisolone group. People on prednisolone alone needed more prednisolone to treat ENL recurrence, but this was likely related to the differences in prednisolone dosing and taper in the two groups.[134] There are case reports in the literature of ENL treated with anti-TNF monoclonal antibodies such as infliximab or a TNF antagonist such as etanercept,[135,136] but these agents are associated with reactivation of *M. tuberculosis* and increased risk of infections, and so could be high-risk in many clinical situations.

Necrotic Vasculitis (Lucio Phenomenon)

"Erythema necroticans" or necrotic vasculitis, also called Lucio phenomenon, is one of the most severe complications of leprosy, with high fatality rates. It is most common in people with diffuse lepromatous leprosy. Diffuse lepromatous leprosy and Lucio phenomenon have been described mostly from Mexico or in people who could have been infected with *M. leprae* or *M. lepromatosis* in Mexico, with isolated cases reported from Asia, Africa, and elsewhere in the Americas.

One case series described clinical and histologic findings in 30 people with diffuse lepromatous leprosy and Lucio phenomenon treated in California between 1969 and 2004. Although this period of time spans different approaches to leprosy multidrug therapy, the series illustrates the diagnostic dilemma encountered in diagnosing diffuse lepromatous leprosy because of its atypical clinical signs, and of determining that the acute presentation of necrotic vasculitis is related to *M. leprae* infection.[57] Although Lucio phenomenon is rare among people with leprosy, it can be fatal, and prompt consideration of leprosy and Lucio phenomenon as part of the differential diagnosis for necrotic vasculitis is essential.[38] The ulcers of Lucio phenomenon are hemorrhagic, indurated, and marginated (Fig. 250.8). The borders are irregularly serrated and the ulceration is concave to the skin. Before ulceration, early lesions may be light blue with an erythematous halo. The number and distribution of infarcts is variable. Earlier in the course of disease, hemorrhagic infarcts tend to be up to 5 cm in diameter and ovoid, whereas later the infarcts are up to 10 cm and more round. Interestingly, in this case series the peripheral leukocyte count was not dramatically elevated.[57] Histologically, biopsies of the skin lesions show foamy macrophages and few lymphocytes. Fite stain generally shows a very high bacterial load. The most helpful histologic feature is the presence of fibrin clots. If neutrophils are present, they are likely associated with necrosis and not with the vascular changes. Superficial dermal vessels are congested with endothelial proliferation, often with thrombosis in the vessels.[57,137]

Immediate treatment for Lucio phenomenon includes supportive care, consideration for sepsis because superinfection of the infarcts is common, and initiation of multidrug therapy for leprosy—including rifampin if not contraindicated, and high-dose corticosteroids. Thrombi and necrosis requiring amputation have been reported. Immunosuppressants other than corticosteroids have been used in some case reports of Lucio phenomenon, but their efficacy has not been proven. Plasmapheresis has been used in cases of necrotic lepromatous vasculitis that do not respond to corticosteroids and supportive care.[138,139] Long-term sequelae of Lucio phenomenon can include scarring, venous insufficiency, and chronic ulcers in addition to the sequelae from leprosy.

Considerations for People With Altered Immunity

Human immunodeficiency virus (HIV) infection dramatically increases the risk of progressing from latent *M. tuberculosis* infection to active tuberculosis, but no such association has been seen for *M. leprae* infection in people with HIV.[140] People with HIV can develop the full spectrum of leprosy disease,[141] although interestingly, studies have suggested that people with HIV may be more likely to present with paucibacillary disease than people without HIV.[141] The timing of clinical disease and development of reversal reactions can be related to immune reconstitution after initiating antiretroviral therapy.[142] In a review of 16 cases of leprosy developing after starting antiretroviral therapy, 10 were characterized as borderline tuberculoid leprosy with reversal reaction. The time from initiation of antiretroviral therapy to diagnosis with leprosy was between 1 and 6 months, the approximate timeframe for development of immune reconstitution.[143] There are no recommended modifications to the leprosy multidrug therapy due to HIV infection, although consideration needs to be made for potential interactions between anti–*M. leprae* and anti-HIV medications. In the case of neuritis occurring independently or as part of reversal reaction, corticosteroids should be started at standard dosing to reduce the risk of irreversible nerve damage.[144]

Anti-TNF agents are used to treat several autoimmune diseases. There are cases of people who developed clinical leprosy after administration of an anti-TNF monoclonal antibody, presumably from the decrease in cell-mediated immune response to the *M. leprae*. Discontinuation of the anti-TNF monoclonal antibody can lead to reversal reaction as the immune system recovers,[145] leading to an immune reconstitution-like reaction. Leprosy and leprosy immune reactions have also been described after solid-organ transplantation[146,147] and during conditioning or immunosuppression for allogeneic stem cell transplantation.[148]

Several immunologic changes related to gestation can alter the course of infections during pregnancy and the postpartum period. Of note, many published studies on leprosy during pregnancy were conducted prior to the use of curative multidrug therapy for leprosy. As such, the natural history of leprosy during pregnancy may have looked different prior to the standardization of multidrug therapy in 1982 than it does in the 21st century. Women may be more likely to be diagnosed with leprosy during pregnancy.[149] This can be related to a decrease in Th1 response to *M. leprae*. One prospective study from Addis Ababa, Ethiopia conducted from 1975 to 1978 reported that of 68 pregnant women with previously diagnosed BL or LL leprosy, 56% had worsening disease during pregnancy and of these, 89% had documented increase in the *M. leprae* bacterial index.[150] Postpartum, the bacterial index reverted in about half of these women. For women who developed ENL, the first episode occurred during pregnancy. For women who developed reversal reaction, the first episode occurred postpartum.[150] WHO guidelines recommend treatment of leprosy with standard multidrug therapy during pregnancy.[80] These medications are known to cross the placenta, and specific risks and benefits should be discussed with the patient before initiating leprosy multidrug therapy.

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251 *Mycobacterium avium* Complex

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SHORT VIEW SUMMARY

Microbiology and Epidemiology

- *Mycobacterium avium, Mycobacterium intracellulare,* and *Mycobacterium chimaera* are closely related organisms grouped into the *Mycobacterium avium* complex (MAC).
- MAC is found in water, soil, and animals but is not spread from person to person.
- MAC most commonly causes pulmonary disease followed by lymphadenitis and disseminated disease, although rare disease presentations are possible, especially in immunocompromised hosts.
- Pulmonary disease typically occurs in older patients with bronchiectasis, chronic obstructive pulmonary disease, or other structural lung disease and is more common in the setting of corticosteroid use. In younger patient populations, pulmonary disease is most commonly seen in the setting of cystic fibrosis.
- Lymphadenitis occurs mostly in children younger than 5 years of age.
- Disseminated disease occurs almost exclusively within immunosuppressed patients, including those with acquired immunodeficiency syndrome (AIDS) and $CD4^+$ cell counts less than 50/mm^3 as well as individuals with malignancy, persons with various autoantibody states or functional cytokine deficits, and those using immune-suppressing medications.

Clinical Manifestations and Diagnosis

- Pulmonary disease diagnosis requires a triad of clinical symptoms, radiographic abnormalities, and positive respiratory cultures.
- Pulmonary disease typically has a chronic presentation with indolent symptoms developing over months to years. Cough is the most common symptom, but low-grade fatigue, anorexia, shortness of breath, fever, and sweats can also be seen.
- Radiographically, pulmonary disease typically has nodular infiltrates with or without cavities. At times it can mimic tuberculosis.
- Lymphadenitis is usually cervicofacial, unilateral, and painless. Diagnosis is via lymph node aspiration or excision. It can be self-limited over time.
- Disseminated disease usually manifests as fever, weight loss, anorexia, and night sweats. Many patients will have acid-fast blood cultures positive for MAC, especially if they are human immunodeficiency virus (HIV) positive. Generalized lymphadenopathy, intraabdominal lymphadenopathy, and lower gastrointestinal tract involvement can be seen.

Treatment (See Tables 251.2 and 251.3)

- Pulmonary disease
  - Diagnosis does not necessitate treatment because many patients can be managed for months to years with pulmonary hygiene, increased caloric intake, and exercise.
  - Treatment for pulmonary disease usually includes a macrolide (azithromycin is favored over clarithromycin), plus ethambutol and a rifamycin (typically rifampin). In cavitary disease or more severe disease, clinicians should consider the addition of an aminoglycoside, usually intravenous amikacin.
  - Treatment duration is based on clinical response and tolerability, but typically pulmonary disease is treated until cultures have been negative for at least 12 months; the usual total duration is 18 to 24 months.
  - Cure of pulmonary disease is difficult, and relapse and reinfection are both common, a context that argues for a chronic disease approach to management.
  - Hypersensitivity pneumonitis may be treated with avoidance of exposure, short-term steroids, or both. It rarely requires antimicrobial therapy.
- Lymphadenitis can be treated with surgical excision or, if this is not possible, with multidrug therapy. In some cases it can be monitored clinically for self-resolution.
- Disseminated disease should be treated with a macrolide plus ethambutol and usually a rifamycin. Individuals with HIV should have HIV therapy initiated as soon as possible. Immune reconstitution inflammatory syndrome may complicate recovery. Consideration should be given to including intravenous amikacin in at least the first 8 weeks of therapy, especially in the non-HIV population. Treatment duration varies based on immune system recovery.
- Skin and soft tissue or bone disease should be treated similarly to disseminated disease, although treatment duration is often shorter and débridement may be needed to provide source control for deeper seeded infections.

Prevention

- HIV/AIDS
  - The classic teaching is that HIV-infected persons with fewer than 50 $CD4^+$ cells/mm^3 should be given weekly azithromycin to prevent disseminated MAC. This can be stopped once $CD4^+$ cell counts are sustained above 100/mm^3.
  - In the new area of effective antiretroviral therapy (ART) for HIV, the duration of $CD4^+$ cells/mm^3 remaining less than 50 after the start of ART is limited, and there is reasonable consideration for holding MAC prophylaxis and only starting HIV treatment.
- Pulmonary disease
  - In individuals with structural lung disease and especially active MAC pulmonary infection, it can be worth avoiding exposure to settings at particularly high risk of aerosolized MAC, such as hot tubs, prolonged soil exposure, and prolonged shower exposure. How much this reduces risk of invasive disease is unclear.
  - When possible in patients with active pulmonary MAC disease or pulmonary MAC colonization, it is worth limiting exposure to systemic corticosteroids, and perhaps even inhaled corticosteroids.
- All disease states
  - Like other mycobacterial diseases, risk of infection and more aggressive disease progression is increased by systemic exposure to anti–tumor necrosis factor-α therapeutics, and these should be avoided when possible in at-risk individuals.

Mycobacterium avium complex (MAC) is the most common of all the nontuberculous mycobacteria (NTM) to cause human infection and pulmonary infection.[1] MAC contains genetically diverse strains with different reservoirs and pathogenicity for humans.[2] The three most common are *M. avium, M. intracellulare,* and *M. chimaera.*[1,3–5] *M. avium* and *M. intracellulare* are often not microbiologically separated and are referred to as *M. avium-intracellulare* (MAI). Two major disease syndromes are produced by MAC in humans: (1) pulmonary disease, usually in adults with some underlying lung disease but whose systemic immunity is generally intact; and (2) extrapulmonary disease, most commonly disseminated disease in patients with advanced immunosuppression such as human immunodeficiency virus (HIV) infection, or localized

cervical lymphadenitis, usually in immunocompetent children.[6] Rarely, MAC can cause disease at other sites, such as cutaneous disease or bone and joint disease.[6] The frequency of MAC pulmonary disease seems to be increasing, especially in older populations, but it is unclear if increases are due to improved microbiologic and radiographic techniques or increased clinician and population awareness leading to increased detection versus true increase in disease incidence.[7–13] Meanwhile, the incidence of disseminated MAC disease, which increased precipitously during the HIV pandemic, has declined with the introduction of effective antiretroviral therapy (ART).[13,14] MAC treatment remains difficult, with prolonged treatment courses and fairly modest success rates, especially in pulmonary disease, for which lung surgery is sometimes needed.[6,15–17] New antimicrobials, antimicrobial combinations, or treatment paradigms are clearly needed for this infection, which has surpassed tuberculosis in incidence and prevalence in many economically developed countries.[6,15–17]

EPIDEMIOLOGY

Reservoir and Route of Acquisition

MAC is composed of environmental organisms thought to be acquired by inhalation, microaspiration, or ingestion.[6] Perhaps due to the low virulence described later, person-to-person spread has not been observed.[6,17] Environmental sites harboring MAC are diverse; they include water, soil, and animals.[6,18–20] MAC has been found to colonize natural water sources as well as indoor water systems, pools, and hot tubs.[19,21] Although specific sites from which individuals acquire MAC are only rarely identified, exposure to recirculating water systems has been described as a specific source of acquisition in human disease, especially in persons with HIV or acquired immunodeficiency syndrome (AIDS).[21–24] However, only a minority of cases can be traced to this source, and this type of connection between exposure and disease has been less clearly documented in the HIV-negative population, suggesting that other environmental reservoirs are important.[4,22,25] Aerosols of natural fresh and salt water as well as dirt particles may contain MAC, and these have been proposed as vehicles leading to transmission of MAC respiratory disease, although aerosolized fluids were not associated with the acquisition of MAC in a case-control study, and other studies have shown a less clear connection between what is in household water and the lungs.[4,18,19,25] Cutaneous MAC infection has been described to occur specifically in relation to hot tub/Jacuzzi use.[6,26] Aerosols from heater-cooler units of heart-lung machines have been specifically documented to transmit *M. chimaera* during open heart surgery, causing a notable global outbreak of these infections, including cases of disseminated disease.[27–29] There is also a strong and growing association between MAC pulmonary disease and gastric reflux disease, and an association with microaspiration, suggesting that this may be the proximate route of entry in many individuals.[30–32] Overall, the ubiquitous presence of MAC in nature makes it difficult to ascertain where an individual patient acquired his or her disease, and except in specific situations this makes avoidance strategies or investigations to identify a source of limited utility.[6]

Pulmonary Disease

MAC pulmonary disease is seen worldwide, although for a variety of reasons prevalence is higher in developed countries, likely in part due to increased life span.[1,3,11,12,33] In the United States and Canada, regional studies have shown an overall disease prevalence of 5 to 19 per 100,000 persons, with prevalence rates potentially as high as 20 to 45 per 100,000 persons in the elderly.[3,8,9,34] Incidence of disease seems to be increasing in many countries, including the United States, Canada, the United Kingdom, and Denmark, and shows substantial geographic variability within countries.[a] Few countries have a national database to accurately evaluate the true occurrence of MAC, although in Denmark where there is complete capture of pulmonary mycobacterial cultures in a national database, the incidence of NTM lung disease (of which 57% are MAC) in 2008 was 1.08 per 100,000 persons.[10] The average age of patients with MAC pulmonary disease in the United States is greater than 60 years, and most patients above this age are women.[5,7,34] However, younger persons with cystic fibrosis (CF) are at significantly increased risk for MAC pulmonary disease, and a causal role has been proposed for this organism in the pulmonary tissue destruction in CF.[37–39] Some specific risk factor(s) for MAC pulmonary disease are present in most cases; these include airway diseases (e.g., bronchiectasis), damage from prior pulmonary infections, structural lung diseases (e.g., chronic obstructive pulmonary disease), and processes that affect the immune systems, such as the use of corticosteroids and other immunosuppressive agents.[9,32] Chronic bronchiectasis is a particularly interesting entity in this regard because it is strongly associated with MAC, but it is still unclear if it is the result of the disease or a predisposition to the disease, as is discussed further later.[9,32,40] These factors, even taken together, do not explain the overall increase in cases of MAC over the past decade.[8]

Extrapulmonary Disease

The most well-known form of extrapulmonary MAC, disseminated MAC (dMAC), was extremely rare before 1980.[41] The heightened susceptibility of patients with HIV/AIDS to this process led to a marked increase, and in 1994 an estimated 37,000 cases of dMAC were seen in patients with AIDS, making this the most common clinical manifestation of MAC at that time.[42–44] With the introduction of effective ART and the increase in ART access, the number of patients with AIDS has declined and with it the number with dMAC.[44–46] The greatest risk for MAC in patients with HIV is with the severe depression of the $CD4^+$ cell count, with dMAC rarely seen in patients with greater than 100 $CD4^+$ cells/mm^3 and the median $CD4^+$ cell count among patients with dMAC and AIDS around 10 cells/mm^3.[47,48] However, there is a spectrum of risk for dMAC that increases as the $CD4^+$ count declines, and the prior occurrence of another opportunistic condition increases the risk for dMAC at any given $CD4^+$ cell level, as does a detectable HIV viral load.[48–50] Children with AIDS have a risk for MAC similar to that of adults, and rates of dMAC have also fallen dramatically in this age group as HIV treatment has improved.[51]

dMAC can also be seen in patients with disease states or medications that cause a mycobacterial-specific immune defect, such as anti–tumor necrosis factor-α (anti–TNF-α) inhibitors, corticosteroids, interferon-γ (INF-γ) pathway defects, *GATA2* mutations, or primary immunodeficiency diseases, such as interferon-γ receptor 1 (IFNγR1) or interleukin-12 receptor β-1 (IL-12Rβ1) deficiency (Table 251.1).[52] While disseminated disease due to innate immunodeficiencies is rare, disseminated disease due to iatrogenic immunosuppression is growing with increasing use of corticosteroids, inhibitors of TNF-α, chemotherapeutic agents, and organ transplants. The combination of anti–TNF-α agents and steroids seems

TABLE 251.1 Genetic Defects Predisposing to Severe Mycobacterial Infections

GENE INVOLVED	INHERITANCE MECHANISM	IMPAIRMENT IN THE IMMUNE RESPONSE
IFNGR1	AD, AR	Impaired IFN-γ response[278]
IFNGR2	AR	Impaired IFN-γ response[279]
STAT1	AD, AR	Impaired IFN-γ and IFN-α response[280,281]
IL12RB1	AR	Impaired T and NK cell function[282]
IL12RB2	AR	Impaired T and NK cell function[283]
ISG15	AR	Decreased IFN-γ production[284]
IRF8	AD, AR	Impaired T and NK cell function[285]
IKBKG	X-linked	Impaired IL-12 production[286]
GATA2	AD, sporadic	Decreased monocytes and dendritic cells[287]
CYBB	X-linked	Decreased oxidative bursts in monocytes and macrophages[288]

AD, Autosomal dominant; *AR,* autosomal recessive; *IL-12,* interleukin-12; *IFN-α,* interferon-α; *IFN-γ,* interferon-γ; *NK,* natural killer.
Modified from National Jewish Health. NTM-TB insights. https://www.nationaljewish.org/NJH/media/ProEd/NTM-TB-INSIGHTS-March-2016.pdf. Accessed May 13, 2019.

[a]References 1, 7, 8, 10, 35, 36.

to confer the most MAC-specific (and mycobacterial disease–specific in general) risk for disease dissemination in comparison to their risk of triggering dissemination of other infections, although pulmonary MAC infection is still the most common entity with anti–TNF-α use.[53–55]

Although less well known than disseminated disease, MAC lymphadenitis is a more common clinical entity in older studies and one that is likely underdiagnosed because many cases of lymphadenitis are not cultured, fail to grow an organism, or never come to medical attention.[56] Before 1980, most nontuberculous lymphadenitis in the United States was due to *Mycobacterium scrofulaceum,* but more recently, MAC has been the cause.[57] MAC cervical adenitis is largely a disease of children younger than age 3 years on the basis of reports from Europe, North America, and Australia.[57–59] A report from children in the Netherlands estimated the incidence of MAC lymphadenitis at 51 cases per 100,000.[59] MAC lymphadenitis is also seen in HIV-infected persons, particularly as "unmasking IRIS" a manifestation of the immune reconstitution inflammatory syndrome (IRIS).[60–62]

MAC skin and soft tissue infection or deeper tendon/joint/bone infection are relatively uncommon entities for which good epidemiologic data are lacking, and are usually related to direct inoculation after puncture wounds, trauma, or surgical incisions.[6] Due to MAC presence in the water and soil, and the association with puncture/trauma, this form commonly involves the hands, and when it does, has a predilection for causing tenosynovitis.[6]

The epidemiology of the relatively newly recognized MAC subspecies, *M. chimaera,* warrants mention here. Although it is generally considered a minimally pathogenic environmental organism, it is now identified as a cause of intravascular infection, primarily as postoperative infections of prosthetic material stemming from a global outbreak, identified in Germany, in which the source of infection was heater-cooler units used in cardiac surgery.[25,27,29] The long incubation time from exposure to disease made diagnosis difficult, with many of the cases diagnosed 1 to 4 years after initial surgery.[27,63] Although the individual risk of infection after such surgery is low, thousands of patients in Europe and the United States were exposed to the contaminated Stöckert 3T heater-cooler devices, prompting a massive effort to locate and treat infected patients.[64] Decontamination of the heater-cooler devices has proven difficult, and it is not completely clear if the outbreak is resolved.[65]

PATHOGEN: CLASSIFICATION AND MICROBIOLOGY

Organisms

Like other mycobacteria, MAC organisms are aerobic, non–spore-forming, nonmotile bacilli. Their cell walls include mycolic acid–containing, long-chain glycolipids, glycopeptidolipids, or both that protect the facultative intracellular organisms from lysosomal attack and give the organisms their "acid-fast" staining characteristic.[6] MAC are classified as "slow-growing" nontuberculous organisms, generally taking 10 to 35 days to grow on solid media and producing smooth-transparent, smooth-opaque, and rough colony variants that are usually light tan in color, although there are variations of uncertain significance.[66] MAC can be cultured on solid or liquid media, with liquid media more sensitive and yielding growth more quickly but not allowing quantification of load.[6] Glycolipid typing has divided MAC into 28 serovars: 1 through 6, 8 through 11, and 21 are *M. avium,* and 7, 12 through 20, and 25 are *M. intracellulare.*[67] There is considerable diversity in the strains of MAC that infect patients, with multiple strains sometimes present in the same patient.[68,69] Advances in molecular genetics have increased the number of subspecies, but the clinical relevance is poorly understood. Distinguishing between MAC species and subspecies is done by using polymerase chain reaction with DNA sequencing, hybridization with specific DNA probes, or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, although depending on the strength of the library there can be some errors seen with MALDI-TOF mass spectrometry.[2,70,71] The identification of *M. chimaera* is relevant in that it does add a prediction of lower virulence for this organism than for MAI in pulmonary infection.[25,72] It is less clear whether there is a relevant difference between *M. avium* and *M. intracellulare,* and since the subspecies cannot be differentiated from each other by traditional biochemical tests, most laboratories group them together as MAI.[6,73]

Virulence

All members of the MAC complex are relatively low-virulence organisms, with *M. chimaera* the least virulent.[6,25,72] Supporting the lower virulence, patients who actually develop true *M. chimaera* pulmonary disease are more likely to be immunosuppressed, have cancer, have received a transplant, or have high inoculum exposure due to infected cardiac surgery equipment.[29,72] There seems to be a difference in virulence between MAC serovars because serovars 1, 4, and 8 are uncommon in the environment but cause most cases of disseminated disease in persons with AIDS.[67] Possible virulence factors include adherence to intestinal epithelial cells, production of catalase, failure to acidify vesicles, and inhibition of phagosome-lysosome fusion.[74–76] MAC has the ability to change colony types in vivo, and this seems related to virulence because clinical isolates from disseminated disease are usually the smooth-transparent colony type, rather than the domed or opaque type.[66,77] Colonies that are smooth and transparent are more likely to replicate in vivo, induce cytokines, and cause more infection in animal models and usually have decreased in vitro susceptibility to antimycobacterial agents.[77–80] There may also be synergy with the HIV virus itself, because isolates from humans with MAC disease can increase cell lysis and stimulate HIV replication in vitro relative to the abilities of animal MAC isolates.[81] It is unclear whether there is a meaningful pathogenicity difference between *M. avium* and *M. intracellulare,* although the largest study in this regard, reviewing 590 patients in South Korea with MAC lung disease, showed statistically more symptomatic, radiographically advanced, and sputum smear–positive disease in the *M. intracellulare* group, as well as less optimal response to treatment.[82–85] However, it is worth noting that this group was also older and had lower body mass index values, suggesting a sicker host.

Pathogenesis

MAC infection starts from primary acquisition of the organism by inhalation/aspiration, ingestion, or direct inoculation. There are specific characteristics of pathogenesis to consider depending on the site of infection.

Pulmonary Disease

MAC pulmonary disease may develop after infection via inhalation/aspiration of MAC from the oropharynx. The duration from acquisition of infection to disease is unknown but presumably occurs over months to years. More than one distinct MAC isolate can be recovered from some patients, suggesting that infection, superinfection, and colonization may occur concomitantly.[69] Grossly, tissue lesions are usually localized, well-circumscribed nodules that at times display cavitary changes. Histologic analysis typically shows poorly formed to well-formed granulomas with surrounding acute and chronic inflammation.[86] Giant cells are seen frequently, and in some cases there is either caseating or noncaseating necrosis.[86] Thoracic lymph node involvement is uncommon.[87] Granulomatous pleuritis, bronchitis, vasculitis, and interstitial pneumonia have also been reported.[86]

Structural lung disease plays an exceedingly important role in the pathogenesis of invasive MAC pulmonary disease.[6,17] The unifying theme in almost all cases is some structural lung abnormality that leads to increased microbial access from the upper to the lower airway, compromised vascular supply and impaired immune surveillance in lower airway segments, and an environment conducive to biofilm formation. This creates a context where an organism of limited pathogenicity can develop to a critical mass necessary to cause invasive disease. Of importance is the role of larger airway disease, with bronchiectasis being a very common comorbidity, seen in up to 85% of patients in recent case series with higher rates in studies with more rigorous radiographic methodology.[9,82,87–90] There is much debate about whether bronchiectasis comes first and predisposes to MAC or whether subclinical MAC infection causes bronchiectasis, but the strong association between the two suggests that the physiology of the both is tightly linked. Once MAC infection is established in bronchiectatic lungs, impaired mucociliary clearance and biofilm formation support infection persistence.[91–93] A handful of known but uncommon causes of bronchiectasis should be considered, including CF, immunoglobulin G deficiency, pulmonary ciliary disorders, connective tissue disease, toxin exposure, and allergic

bronchopulmonary aspergillosis.[94] Most nonbronchiectatic cases of pulmonary MAC are in the setting of obstructive lung diseases (e.g., emphysema) or fibrotic lung diseases treated at least intermittently with immunosuppression.[6,9,90] In these cases, MAC preferentially infects damaged lung, with cavity-like superinfection of bullous emphysematous areas a common finding. Inhaled corticosteroids probably play an additive role by causing airway immunosuppression, with recent data suggesting an association between use and pulmonary MAC disease.[95–97]

Extrapulmonary Disease

Disseminated disease usually starts by ingestion of MAC, followed by localized disease in the lung or gut, with the gut more common. Dissemination then ensues from one of these locations over several months.[98] The organisms penetrate the gut wall and subsequently are phagocytized by macrophages and other reticuloendothelial cells.[99,100] Most disseminated disease is due to a single strain, but multiple distinct isolates have been recovered from up to 15% of patients.[68] Histologically, epithelial cells show only mild inflammatory changes and ulceration is uncommon.[100] Foamy macrophages fill the lamina propria, where these massively infected cells packed with bacilli may expand the intestinal villi, giving an appearance similar to Whipple disease.[100] The resulting thickening of the bowel wall can rarely lead to intussusception, gastrointestinal hemorrhage, or obstruction. Mesenteric adenopathy ensues with poorly formed granulomas and at times neutrophilic necrosis.[101,102] Subsequent hematologic dissemination can then occur and while any organ can be seeded, the most common sites are liver, spleen, and bone marrow.[102,103] The mycobacterial burden in bacteremia is variable, ranging from 1 to greater than 10^5 colony-forming units/mL.[104,105] MAC bacteremia leads to elevated serum levels of TNF-α and interleukin-6, which are likely responsible for the predominant symptoms of fever, night sweats, and cachexia.[106,107] The mechanism of the severe anemia frequently seen in dMAC is not well understood because bone marrow involvement is not always present, erythropoietin levels are variable, and clinical response to exogenous erythropoietin is unpredictable.[108] A unique pathophysiologic abnormality that can be seen with dMAC is asymptomatic but marked elevation of serum alkaline phosphatase with little elevation of transaminases, bilirubin, or other parameters of hepatic function.[109,110] Liver histology in these cases is unremarkable, suggesting interference with enzyme metabolism rather than hepatic destruction. In the setting of HIV/AIDS, when ART is instituted, a vigorous granulomatous response results in elimination of bacilli from the tissues, but also causes a period of marked lymph node enlargement while this process occurs—IRIS, as seen in MAC and HIV/AIDS.[60–62,111,112] Untreated, dMAC ultimately leads to death by generalized wasting.

The other common form of extrapulmonary MAC, cervical lymphadenitis, is likely acquired through ingestion of MAC and spread to local lymph nodes, where disease can develop in the setting of relative but not extensive immunosuppression, such as childhood.[56] Lesions again reveal granulomas. Ulceration and cutaneous fistula formation are frequent complications, particularly when nodes have been aspirated or biopsied.[113] In the immunologically "normal" host, nodes are often single and dissemination of disease does not occur. Without treatment, the nodes usually go through a process of purulent drainage after 4 to 8 weeks followed by self-resolution by the 1-year mark in most, leaving only a small scar at the site of infection.[114] In the less common skin, joint, or bone infections, direct inoculation leads to infection followed by local granulomatous response and adjacent spread of disease. Again, dissemination in this setting is uncommon.

Host Immunity

Pulmonary Disease

The fact that many cases of pulmonary MAC disease occur in persons with a history of airway disease suggests that impaired pulmonary clearance mechanisms predispose to disease. These patients typically do not have a profoundly impaired immune response and show acceptable delayed hypersensitivity to MAC antigens as well as adequate humoral and cell-mediated immune responses.[115] The TNF-α pathway appears to have significant importance in pulmonary disease control given the increased rates of pulmonary infection in hosts taking TNF-α inhibitors.[54,55] Although there is an increased risk of dissemination with these agents, especially in combination with corticosteroids, this is still rare and most disease remains localized.[54,55]

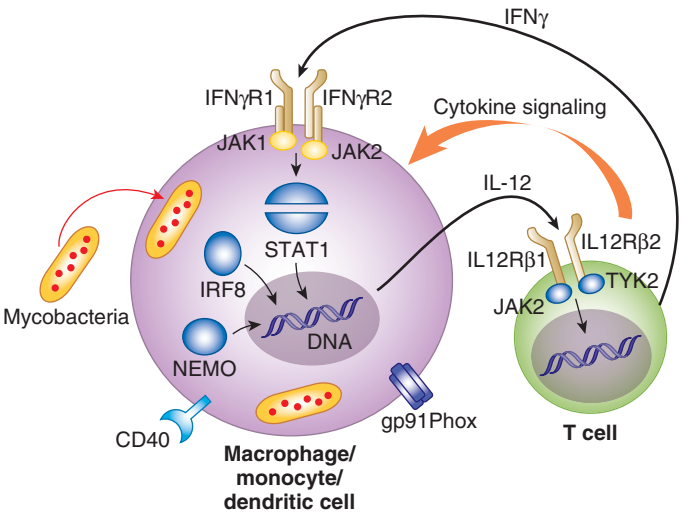

FIG. 251.1 Impaired cytokine production by T cells in patients with HIV/AIDS leads to failure of macrophage activation to eliminate intracellular *Mycobacterium avium* complex. *CD40,* Cluster of differentiation 40; *gp91Phox,* glycosylated polypeptide 91^{phox}; *IFNγ,* interferon-γ; *IFNγR1,* interferon-γ receptor 1; *IFNγR2,* interferon-γ receptor 2; *IL-12,* interleukin-12; *IL12Rβ1,* interleukin-12 receptor β-1; *IL12Rβ2,* interleukin-12 receptor β-2; *IRF8,* interferon regulatory factor 8; *JAK1,* Janus kinase 1; *JAK2,* Janus kinase 2; *NEMO,* nuclear factor kappa B essential modulator; *STAT1,* signal transducer and activator of transcription 1; *TYK2,* tyrosine kinase 2. *(Modified from National Jewish Health. NTM-TB insights. https://www.nationaljewish.org/NJH/media/ProEd/NTM-TB-INSIGHTS-March-2016.pdf. Accessed May 13, 2019.)*

Extrapulmonary Disease

In addition to the increased risk of disseminated infection due to TNF-α inhibitors, systemic steroids, or both, individuals with inherited defects in the IFN-γ signaling pathway are exquisitely susceptible to dMAC, confirming the importance of this cytokine in host defense against MAC (see Table 251.1). Currently known defects include the IFN-γ receptor ligand-binding chain, the IFN-γ signal-transducing chain, defective IL-12–mediated modulation of IFN-γ production, and signal transducer and activator of transcription 1 (STAT1) abnormalities, which also impair IFN-γ, as well as TNF-α, response.[52] Additionally, as mentioned previously, *GATA2* mutations and primary immunodeficiency diseases, such as IFNγR1 or IL-12Rβ1 deficiency, predispose to poor mycobacterial disease control and disseminated infection.[52]

In patients with HIV/AIDS, cytokine production by T cells is severely impaired leading to failure of macrophage activation to eliminate intracellular MAC (Fig. 251.1).[116,117] While MAC-specific T cells develop during disseminated disease in AIDS, they do not control the pathogen.[103] Cytotoxic $CD4^+$ cells are also important in inhibiting intracellular replication of MAC, but their function is impaired in HIV infection.[118] Additionally, antibodies against MAC are produced in response to disease in normal hosts but not in patients with AIDS.[49] Although the role of these antibodies is unclear, they do increase MAC killing in vitro.[119] Other nondisseminated extrapulmonary disease states, such as lymphadenitis and skin and soft tissue infections, demonstrate generally intact humoral and cell-mediated immunity and robust noncaseating granulomatous response to infection.

CLINICAL MANIFESTATIONS

Pulmonary Disease

The clinical presentation of pulmonary MAC disease is nonspecific and can be confused with other chronic pulmonary diseases.[6] Features of pulmonary disease vary only slightly between patients whose respiratory cultures grow *M. avium* and *M. intracellulare,* but *M. chimaera* is more often a transient colonizer.[72] The classic presentation of pulmonary

MAC is one of a subacute-to-chronic illness occurring in individuals with a known or previously unknown history of underlying pulmonary pathology.[6,73] Other features that may be identified on a chest radiograph in patients with pulmonary MAC are pectus excavatum and scoliosis, with pectus excavatum 3 to 10 times and scoliosis 2 to 3 times as common as in the general population.[6,120,121] Pleural effusions are very rare.[122,123] MAC pulmonary disease is bilateral in most cases and while the percentage with cavitary disease varies by cases series, more recent data suggests 15% to 35% of cases have some cavitary component.[124–127] The cavities in patients with MAC are more likely to be thin walled than in tuberculosis, may be quite large (most 2–5 cm), and may initially have been caused by another disease before being superinfected by MAC (Fig. 251.2).[122,128] Tree-in-bud opacities are seen often, but these are not specific for MAC. Bronchiectasis or other underlying lung disease is increasingly recognized as present in most individuals, as discussed further later (Fig. 251.3). Since bronchiectasis also predisposes this patient population to colonization with other microbes that can act as pathogens, flares in disease due to these organisms can mimic flares due to MAC.[6,17] Initial data out of the bronchiectasis registry suggest that *Pseudomonas* colonization in particular portends a more difficult bronchiectasis course, and interestingly, *Pseudomonas* is less commonly found in patients with MAC than bronchiectatic patients without NTM.[32,129] Other NTM can also be found with *Mycobacterium gordonae,* a common colonizer that is also almost never a pathogen, and *Mycobacterium abscessus* complex, found in roughly 20% to 30% of cases, sometimes as a coinfection.[130,131]

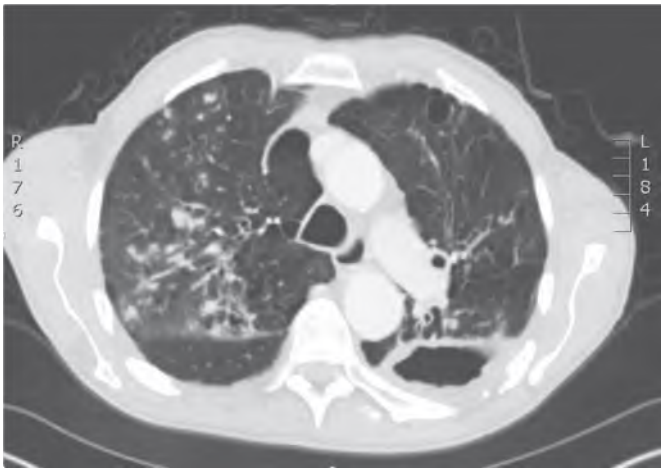

FIG. 251.2 Fibrocavitary pulmonary *Mycobacterium avium* complex in a male patient with a smoking history predisposing to underlying emphysema and bronchiectasis. Pleural thickening, nodular tree-in-bud opacities, and bullous changes of emphysema are also present.

FIG. 251.3 Nodular bronchiectatic pulmonary *Mycobacterium avium* complex in an elderly woman with bronchiectasis showing the tree-in-bud opacities than are often seen in this disease.

There seem to be two general phenotypes in this disease, although the understanding is evolving and there is significant overlap. The more common phenotype is in thin, middle-aged to elderly women with no previously known lung disease, although bronchiectasis is often found during the evaluation.[9,34,90,132–134] This syndrome is sometimes referred to as "the Lady Windermere syndrome," for the principal character in Oscar Wilde's play, although this phenotype has been more recently described in males as well.[133,135] The syndrome has been increasingly recognized over the last 30 years, likely due to a combination of increased physician awareness, improved diagnostics, and increased awareness in the general population.[136] Patients with this syndrome usually present with chronic cough, but other constitutional symptoms, such as weight loss, fever, sweats, and fatigue, can be mild and indolent.[6,82] Chest radiography may have minimal abnormalities that often wax and wane in extent over years.[122,137–139] Most patients have underlying bronchiectasis that is identified much more readily on chest computed tomography (CT) than chest radiography, but even on CT the findings can wax and wane with time.[122,126,137,138,140–142] The CT finding of bronchiectasis combined with multiple nodular infiltrates most prominently in the right middle lobe and lingula is particularly suggestive of MAC pulmonary disease (Fig. 251.4).[6,122]

The less common earlier described phenotype is shifted toward middle-aged men, frequently with a history of heavy smoking and usually with previously known and significant underlying structural lung disease.[6] The clinical picture is also one of a chronic disease, but the symptoms are often more overt, including productive cough in most, weight loss or weakness in a substantial number, and a minority with fever or night sweats.[6,127,143] Inflammatory markers are more often elevated.[128] Chest radiographs in this chronic form of pulmonary MAC typically show upper lobe fibronodular and cavitary disease, which may be associated with pleural thickening (see Fig. 251.2).[6,122,127] Rates of cavitation can be higher than with tuberculosis, likely due to superinfection of bullae or damaged lung parenchyma that is already present.[6] Of note, the all-cause mortality in this disease form seems to be much higher than in the nodular bronchiectatic disease described earlier, likely due to a sicker host.[6,125,127]

Patients with CF are frequently colonized with MAC or other NTMs, but the clinical importance of MAC in individual patients can be difficult to discern. In one multicenter prevalence study of 986 patients with CF, 13% had at least one of three sputum samples positive for NTM, most (72%) with MAC, and similar findings have been replicated in other studies.[37–39,144] Overall, individuals with CF and MAC had similar pulmonary function tests compared with patients without MAC, suggesting that it is non–disease-causing colonization in at least some individuals.[145] Serial CT scans provide important information because

FIG. 251.4 Dense bronchiectasis of the right middle lobe and lingula that is classic for pulmonary *Mycobacterium avium* complex in a woman with a longer history of nodular bronchiectatic disease. The areas of dense bronchiectasis and surrounding inflammation can be difficult to penetrate with antimicrobial therapy and sometimes require lung surgery to adequately address.

patients with MAC identified by culture and progression of CT abnormalities are more likely to have clinical decline than other CF patients with MAC.[145] CT abnormalities suggestive of progressive MAC in CF include of areas of cystic or cavitary disease, subsegmental or larger areas of consolidation, pulmonary nodules, and tree-in-bud opacities.[145] The current standard is to use the same diagnostic and treatment criteria for MAC as are used in patients without CF, although the popularity of chronic azithromycin treatment in CF has raised additional concern about azalide/macrolide resistance.[38,146,147]

Hot tub lung—another rare, although well-known, pattern of MAC pulmonary disease—is less infectious and more inflammatory in nature, typically occurring in persons exposed to pools of heated water containing MAC.[148–151] It is presumed that in these cases inhalation of aerosolized MAC results in a hypersensitivity pneumonitis.[148–151] Individuals present with mild-to-moderate dyspnea and dry cough, with or without fever. Chest radiographs and CT scans show patterns similar to other hypersensitivity pneumonitides, including bilateral alveolar infiltrates, centrilobular nodules, and ground-glass opacities.[152,153]

Extrapulmonary Disease

dMAC occurs exclusively in persons with advanced immunosuppression, with dMAC in HIV/AIDS being the classic example, and if untreated is fatal. A natural history study of patients with HIV infection found that MAC bacteremia developed at a median $CD4^+$ count of 13 cells/mm^3, almost always in patients with an uncontrolled viral load, and the median survival after diagnosis was only 134 days.[48] In such cases, it can be difficult to separate features directly attributable to MAC from abnormalities attributable to advanced HIV/AIDS, but some clue is provided by a study evaluating patients at risk, in which prospective monthly blood cultures for MAC showed that most changes occurred in the first 2 months of positive MAC blood cultures.[154] The presentation generally includes high fever, weight loss, night sweats, and severe anemia (hematocrit <25%).[109,154,155] Other features associated with MAC include abdominal pain, diarrhea, intraabdominal lymphadenopathy, hepatosplenomegaly, leukopenia, and an elevated serum alkaline phosphatase level.[109,155] Many different organs can be involved, with a comprehensive autopsy series of 44 patients with HIV/AIDS and dMAC showing most common involvement of the spleen, lymph nodes, liver, intestines, colon, and bone marrow and less common involvement of the lungs, adrenal glands, and stomach and rarely the central nervous system.[156] Patients with HIV/AIDS and dMAC only rarely have pulmonary disease with parenchymal lung involvement, occurring in less than 10% of patients.[98,157] dMAC can also be seen in individuals with underlying immunodeficiencies (e.g., Table 251.1) or in those on immunosuppressive therapy, especially high-dose corticosteroids, TNF-α, or both, and the clinical presentation is generally similar.[41,52,54,158,159] Given declines in AIDS incidence in many developed countries, as well as increased use of immunosuppressive drugs, these may become the more common forms of dMAC in some populations. Due to the nonspecific manifestations with dMAC, the differential diagnosis is broad and depending on the host and epidemiology, disseminated disease due to other mycobacterial and fungal granulomatous diseases as well as lymphoma and, in HIV patients, AIDS wasting syndrome should be considered.

Local manifestations of dMAC may occur in patients with severe immunosuppression who have immune reconstitution. This usually happens either in the case of ART initiation in HIV patients or in the case of withdrawal of immunosuppressive therapy in other patients, and leads to IRIS or a "paradoxical reaction" as described earlier in this chapter.[60–62,111] Especially in HIV/AIDS, this can manifest as painful lymphadenopathy occurring in the first 3 months of initiating ART, while abdominal pain, hepatosplenomegaly, and pulmonary-thoracic disease have been reported to occur in roughly 25% of cases.[62,111] IRIS symptoms differ from those of dMAC itself; fever may be present, but constitutional symptoms (e.g., weight loss, night sweats) are usually absent, and blood cultures do not grow MAC.[61,62,111] Since these patients are at risk for many etiologies of these symptoms, biopsy may be required to establish an accurate diagnosis.

Cervicofacial lymphadenitis is the most common localized extrapulmonary manifestation of MAC and is usually seen in children, with at least 80% of individuals between 1 and 5 years of age.[57,59,160] Tuberculosis as a cause of lymphadenopathy is much more common than MAC in adults.[161] MAC lymphadenitis is usually painless or minimally painful unilateral enlargement of a node in the submandibular or high jugular region.[57,59,160,162] Nodes are often firm, varying from 1 to 7 cm in diameter, with the mean size in one series reported as 2.5 × 3 cm.[161,162] Bilateral disease is rare and multiple nodes are involved in less than 20%. The disease almost always stays localized absent significant immunocompromise, and systemic symptoms such as fever are uncommon.

MAC, while uncommon, is still the most commonly reported NTM to cause cutaneous disease.[163] Cutaneous MAC occurs in both immunocompetent and immunocompromised hosts and is difficult to differentiate from other chronic skin lesions.[164,165] Cutaneous MAC is generally due either to direct inoculation of the skin by trauma, surgery, or injection or to cutaneous seeding in disseminated disease.[166–168] When it occurs, cutaneous lesions may be indolent ulcers, nodules, or plaque with local swelling, erythema, tenderness, and infection of deeper tendons (especially with hand involvement), but little local lymphadenopathy and few systemic symptoms.[165,168] MAC is also a rare cause of osteomyelitis, mastoiditis, renal disease, prostatitis, peritonitis, corneal ulceration, mastitis, septic arthritis, and synovitis. MAC osteomyelitis can rarely develop in HIV-infected patients with dMAC, and vertebrae are the most common bone involved.[169] Osteomyelitis may clinically present later as patients develop immune reconstitution with initiation of ART.[169] In the non-HIV population, cases of osteomyelitis are even more rare, often vertebral, and usually either due to direct inoculation or associated with medication-induced immunosuppression.[170,171]

DIAGNOSIS

Pulmonary Disease

Diagnosis of MAC pulmonary disease is difficult because of the frequency of positive sputum cultures among persons without overt disease.[6] A single sputum culture that grows MAC has a marginal positive predictive value for clinical disease and as a result the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) have developed a generally accepted case definition for pulmonary MAC disease.[6,9,17] In this definition's criteria, patients must have symptoms compatible with MAC pulmonary disease, have abnormalities on chest imaging compatible with MAC pulmonary disease, and have one of the following microbiologic features: (1) two positive MAC sputum cultures; (2) a bronchoalveolar lavage with a positive culture for MAC; or (3) acid-fast bacilli (AFB) or granulomas, or positive MAC culture from a histopathologic specimen (if MAC is not cultured from the biopsy, MAC should be present in at least one sputum or bronchoalveolar lavage sample).[6]

AFB sputum smears are neither sensitive nor specific in the diagnosis of pulmonary MAC disease because they are rarely positive and, when positive, sometimes represent other acid-fast organisms.[6] Cultures usually turn positive by 35 days when performed on solid media and by 10 to 21 days when performed in broth, but growth time depends on the inoculum size and cultures cannot be classified definitively as negative until 6 weeks.[6] Cultures contaminated with bacterial or fungal overgrowth before 6 weeks cannot be interpreted and should be repeated. Patients who do not meet the diagnostic criteria should be followed and reevaluated because clinical disease may develop over time.[39,125,126,172–174] Occasionally treatment should be pursued without meeting all diagnostic criteria if there are very compelling clinical features to support either aggressive treatment or chronic suppressive therapy (i.e., profound immunosuppression, other severe lung disease with limited pulmonary reserve).

For hypersensitivity pneumonitis due to MAC, diagnosis is usually clinical based on a combination of exposure history, chest imaging, and sometimes lung pathology. Patients usually give a history of recent and sometimes extensive exposure to aerosols from pools or hot tubs.[6,153] Chest radiographs may be normal, may show nodules or infiltrates, or in the acute presentation, can show total opacification of the lung fields.[148,152,153] In the acute stages, lung biopsy may show neutrophilic or lymphocytic infiltrates; later, noncaseating granulomas may be seen.[153] Patients with hypersensitivity pneumonitis may grow MAC from sputum, bronchoalveolar lavage, or lung biopsy specimens and this entity may be a combination of early infection and hypersensitivity, but patients

frequently do not develop chronic infection with MAC.[6] No test for serum precipitins to MAC antigens analogous to that for allergy-mediated *Aspergillus* pulmonary disease is currently available.

Extrapulmonary Disease

Disseminated extrapulmonary MAC is diagnosed by recovery of MAC from blood or another usually sterile site (e.g., bone marrow, liver, or spleen).[6] Since growth from lymph nodes may represent localized disease and growth from sputum, bronchial washings, gastrointestinal biopsy specimens, or stool can represent either colonization or localized disease, in such cases positive cultures from more than one organ are necessary to establish a diagnosis of disseminated disease.[6] Isolation of MAC from stool by itself does not indicate disease and should not be used in clinical diagnosis.[6] In patients with HIV/AIDS, blood is the preferred specimen for diagnosis of dMAC and is the method of diagnosis in more than 90% of cases, with one specimen having a diagnostic yield around 90% and two specimens a yield near 99%.[6,175,176] One caveat is that in early disease, bone marrow biopsy with culture may be more sensitive.[103] Blood cultures are also the test of choice for disseminated disease in non–HIV infected hosts, but less is known about the test characteristics in this setting. Blood culture technique should be that of AFB cultures because MAC will not grow in standard blood culture media, and lysis-centrifugation systems to quantify bacterial load have limited clinical utility.[6,176] When the burden of bacteremia is high, mycobacteria may be seen on Kinyoun or auramine stain of buffy coat smears, but this is neither sensitive nor specific. Direct detection of MAC in blood by polymerase chain reaction may be as sensitive and specific as culture, but this assay is not widely available.[177,178]

The diagnosis of MAC lymphadenitis requires growth of MAC from the involved node and a compatible clinical syndrome.[6] Excision is preferred to needle biopsy because fistula formation is common after needle biopsy.[6,113,114] Histologic examination is important and typically reveals noncaseating granulomas with or without AFB, but should be interpreted within the clinical context.[6,113,179] Isolated lymphadenopathy has a large differential diagnosis, as mentioned previously, so workup for other entities is often warranted. Lymph nodes reactive to local bacterial infections, concurrent viral infections, other granulomatous infection, and malignancy should be considered.

Diagnosis of MAC disease in other sites, such as skin, soft tissues, bones, and joints, may be suggested by the finding of AFB or tissue granulomas, but confirmation requires recovery of MAC by culture of the affected site and a compatible clinical syndrome since MAC has the potential to be a nonpathogenic colonizer of nonsterile body sites, as mentioned earlier.[6,179]

TREATMENT AND PREVENTION

Principles of Treatment

Successful treatment of MAC is a challenge and is highly influenced by the site of infection, the immune status of the host, and the host's ability to tolerate antimicrobial therapy. As with therapy of other mycobacterial infections, the use of at least two, and usually three, active drugs is essential to prevent emergence of resistance and improve outcomes.[6,17,180] Therapy is made difficult by the paucity of antibiotics that are highly active against MAC, by the frequency of adverse effects associated with available antibiotics, and by some lack of clarity around what outcome metric best represents "success".[181] In pulmonary MAC disease, given the difficulty providing curative therapy and the prolonged antibiotic courses needed, patient-related quality of life and the way this is affected by both the disease and the therapeutic interventions are important considerations.[6,182] At times a less effective antibacterial approach may be the most appropriate choice for an individual patient, although in general effective antimicrobial treatment seems to improve quality of life in this population.[6,182–184] Since disseminated disease carries much higher and more rapid morbidity and mortality, every effort should be made to provide aggressive curative therapy and reduce the immune defect that predisposed to dissemination.[6]

Specific Antimicrobials

Macrolides and their subclass azalides (hereafter all referred to as macrolides) exhibit excellent in vitro activity against MAC and have revolutionized the treatment of MAC disease.[185–189] Although clarithromycin has lower minimal inhibitory concentrations (MIC), azithromycin is at least as active, if not more active, in vivo than clarithromycin (likely due to better tissue penetration), and the two have equivalent clinical outcomes.[6,17] Additionally, azithromycin has fewer drug-drug interactions, its levels are less affected by rifamycins, and it is dosed once daily versus twice daily for clarithromycin, generally making it the macrolide of choice for MAC.[190,191] An important point about macrolides is they are the only drug class for MAC treatment with proven correlation between drug susceptibilities and clinical outcomes, making macrolide drug susceptibility testing an important part of management.[6,17,192] Roughly 99% of strains of MAC from patients not previously given a macrolide are susceptible to clarithromycin or azithromycin.[193–195] Prior macrolide exposure, especially macrolide monotherapy, has implications because significant resistance can develop in this setting.[194,196] This resistance develops more quickly in disseminated than pulmonary disease, likely due to higher disease burden and more metabolically active organisms in disseminated disease.[193,197] Treatment outcomes are significantly worse if resistance develops, so efforts to mitigate macrolide resistance are a central tenant of MAC management.[6]

Other drugs have been shown to have clinical activity against MAC as well. Ethambutol has in vitro activity against MAC, has proven efficacy in reducing mycobacteremia for HIV/AIDS patients with dMAC, and is part of most recommended MAC regimens.[6,185,198] Ethambutol is probably the second most important drug in MAC regimens because it is more effective than any other class, including rifamycins, in protecting against the development of macrolide resistance.[199–202] Ethambutol in combination with a macrolide is the only two-drug regimen allowed by the 2007 ATS/IDSA guidelines for treatment of certain forms of MAC lung disease and a pragmatic randomized, multicenter clinical trial comparing this two-drug therapy with standard three-drug therapy for pulmonary MAC has been funded.[6,191] Every effort should be made to include ethambutol, dosed at 15 mg/kg/day, or 25 mg/kg three times/week, in MAC combination therapy.[6] Rifamycins are active in vitro against MAC, and clinical outcomes in both pulmonary MAC disease and dMAC have improved with addition of rifamycins to the regimen.[185,201,203,204] Given their long-term tolerability and increased efficacy data compared to other options, they are the third drug added to MAC treatment regimens that make up guideline-directed therapy.[6,17] Although it is not proven that MICs of ethambutol or rifamycins are associated with clinical outcomes, there are some suggestive emerging data and we would suggest taking their MICs into account.[205] In many ways aminoglycosides, with amikacin usually the most active of the class, are the most effective MAC therapeutics against susceptible isolates and improve treatment outcomes when used.[6,192,206] However, aminoglycoside toxicity and the lack of oral formulations limit use.[6,207] For more severe disease in which the debilitation of illness offsets the risk of toxicity and need for prolonged intravenous access, they become the additional drug of choice for an induction phase of therapy as discussed in more detail later.[6] When used for induction therapy, aminoglycosides can generally be given three times weekly, which makes this therapy more feasible and tolerable for many patients.[6,207]

The most relevant additional oral antibiotics in cases of failure or intolerance of first-line regimens include clofazimine, fluoroquinolones (FQs), oxazolidinones (linezolid and tedizolid), and bedaquiline.[208–213] Clofazimine is the most intriguing agent in this group, with the most reliably low in vitro MICs and an acceptable long-term safety profile known from the leprosy treatment experience.[190] However, early clinical data from dMAC treatment in HIV/AIDS patients showed higher mortality rates in clofazimine-containing arms, raising concern about this drug and leading to a black box warning for use in HIV/AIDS.[200,214,215] When this literature is critically assessed, the patients in the clofazimine arms in these trials may have been sicker or clofazimine may have been combined with less effective antibiotics versus the comparator groups, and there is no strong physiologic basis for the worse outcomes; therefore there is reason to think this risk may be overstated, especially since other studies show no difference in outcomes.[216] However, it is still generally recommended that the drug not be used for dMAC in HIV/AIDS.[6,217] There are promising case series using clofazimine for other forms of MAC, especially pulmonary disease, but robust, controlled

clinical data are currently lacking, although one monotherapy randomized controlled trial for pulmonary MAC is ongoing (NCT02968212).[208,210,218,219] It is important to note that if clofazimine is used at standard dosing of 50 to 100 mg daily, the long half-life means it takes roughly 60 days to reach therapeutic steady state.[220,221] FQs have a robust body of supporting literature in tuberculosis, but MICs for MAC are generally high due to baseline resistance, and they should not be used unless there are favorable MICs from a reputable laboratory.[190,222] Moxifloxacin has the most in vitro activity of all the FQs against MAC and is the FQ of choice if they are to be used.[190,222] There are concerns that FQs do not adequately protect macrolides against the development of resistance and may even have some antagonism with macrolides.[6,223] As such, FQs should never be used in combination with macrolides as a two-drug combination in the treatment of MAC disease.[6] A third active drug must be included. Oxazolidinones and bedaquiline are used in treatment of resistant tuberculosis and generally have in vitro activity against MAC. There are now limited but promising data from case series in their use for MAC, especially pulmonary disease.[209–211,224,225] Given the smaller body of data for their use, and their often treatment-limiting toxicities, they are generally reserved for use in macrolide-resistant pulmonary MAC or salvage pulmonary MAC cases, as described later.

In the pre-macrolide era, quoted "success rates" for pulmonary MAC treatment were no better than 50%, with longer treatment regimens and higher rates of drug toxicity.[6,226,227] HIV/AIDS patients with dMAC also responded poorly, with high mortality, to non–macrolide-containing regimens.[228,229] Even with therapy in the macrolide era, response rates are still lower than ideal and treatment courses are long, probably in part because we still do not understand optimal pharmacokinetic and pharmacodynamic considerations for this disease or the optimal way to assess treatment response.[181,190,230] In pulmonary MAC over the last 20 years, patients who have tolerated 6 or more months of macrolide therapy show sputum conversion rates ranging from 60% to 90%, with other clinical end points such as durable culture conversion and radiographic resolution less common.[186,187,231–234] Most patients in these studies received ethambutol, a rifamycin, and sometimes an aminoglycoside in addition to the macrolide. Even in the macrolide era, treatment outcomes for dMAC in HIV/AIDS can still be poor in the initial year after diagnosis, likely influenced by socioeconomic and racially based disparities in resources and among those who get the disease, but in those who survive the first year, long-term good outcomes can be achieved with MAC treatment and durable ART.[235,236]

Antimicrobial Tolerability

The maximal dose of clarithromycin is 500 mg twice daily, and higher doses have been associated with poorer clinical outcomes and should not be used unless guided by therapeutic drug monitoring.[193,216] Many patients have difficulty tolerating 500 mg twice daily of clarithromycin because of gastrointestinal side effects and dosing frequency, which is an advantage of 250 mg of daily azithromycin, for which the side effect profile and dosing schedule are more favorable.[237] When gastrointestinal side effects occur, they are often time limited, but if not, they can sometimes be mitigated by decreasing dosing frequency to three times weekly, at an increased dose of 500 mg, although this is not usually recommended in severe or disseminated disease (Tables 251.2 and 251.3).[233] Azithromycin also causes fewer drug-drug interactions than clarithromycin, making it more feasible to use in individuals on multiple medications.[238] Ethambutol is well tolerated by most patients, although at higher doses, gastrointestinal intolerance may occur. The main toxicity concern with ethambutol is optic neuritis, making baseline evaluation and serial symptom monitoring for ocular symptoms while on therapy warranted, although we do not think serial ophthalmologic examination is needed in the absence of symptoms with standard lower dosing (15–20 mg/kg/d or 25 mg/kg three times/week).[6,239] Since rifabutin is associated with higher rates of gastrointestinal distress, liver function abnormalities, neutropenia, and less commonly uveitis and severe arthralgias, rifampin has become the rifamycin of choice for MAC treatment due to better tolerability.[6,240] The most common side effect with rifampin is still gastrointestinal intolerance, although this often improves after the first few weeks on therapy, and can be managed with antinausea therapy or by taking the medication with food (even though drug absorption is slightly impaired by this).[6] The most problematic issue with rifamycin use is drug interactions, as discussed later. All the rifamycins turn body fluids (particularly urine) a reddish-orange color—a benign issue that will resolve once therapy is completed.[6]

Aminoglycosides have no oral formulation and in almost all cases must be administered parenterally, although streptomycin is usually given intramuscularly.[6] However, patients frequently become intolerant of the injections associated with long-term streptomycin treatment, so the availability of long-term intravenous access makes amikacin the preferable agent.[6] Administration of aminoglycosides twice weekly or three times weekly is adequate for treatment of MAC in most forms and lessens inconvenience as well as drug toxicity.[207] The major toxicities of aminoglycosides are hearing loss, vestibular dysfunction, and renal function impairment. When amikacin, kanamycin, or streptomycin is given daily at 15 mg/kg or three times weekly at 25 mg/kg, ototoxicity has occurred in roughly 35%, nephrotoxicity in 15%, and vestibular toxicity in 10% of MAC patients.[207] We recommend starting at 10 to 15 mg/kg three times weekly to limit these toxicities further and increasing the dose until the peak serum concentration–to-MIC (C_{max}/MIC) ratios are in the estimated optimal range of 3 to 5.[6] Given the complexity, expert consultation is recommended to achieve optimal dosing.[6] Aminoglycoside hearing loss is usually permanent, so audiometry should be performed at baseline and repeated monthly in all patients on systemic aminoglycoside therapy for MAC.[6] Similarly, serum creatinine levels should be followed either weekly or every other week.

Clofazimine toxicity is most commonly gastrointestinal, although almost all patients will also experience darkening of the skin as is well described in the leprosy literature.[6,208,218] Prolonged FQ use likely increases the already known chances of quinolone-associated tendinopathy,

TABLE 251.2 Initial Regimens for Pulmonary *Mycobacterium avium* Complex

MILD TO MODERATE NODULAR/ BRONCHIECTATIC DISEASE	CAVITARY OR ADVANCED/SEVERE DISEASE
Azithromycin 250 mg PO daily or 500 mg PO three times weekly[b]	Azithromycin 250 mg PO daily[c]
Ethambutol 15 mg/kg PO daily or 25 mg/kg PO three times weekly	Ethambutol 15 mg/kg PO daily
Rifampin 10 mg/kg (600 mg max.) PO daily or three times weekly[d]	Rifampin 10 mg/kg (600 mg max.) PO daily[e] Amikacin 10–15 mg/kg IV three times weekly[f]

[a]See text for full dosing recommendations.
[b]Alternative: clarithromycin 500 mg PO twice daily or 500 mg three times weekly.
[c]Alternative: clarithromycin 500 mg PO twice daily.
[d]Alternative: rifabutin 300 mg PO daily or 300 mg PO three times weekly.
[e]Alternative: rifabutin 300 mg PO daily.
[f]Alternative: Streptomycin 10–15 mg/kg IV or IM three times weekly.
Modified from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. *2007;175:367–416.*

TABLE 251.3 Optimal Serum Drug Levels for Antibiotics Used in the Treatment of MAC

ANTIMICROBIAL	OPTIMAL SERUM LEVEL (mcg/mL)[b]
Azithromycin	0.2–0.7
Clarithromycin	2.0–7.0
Rifampin	8.0–24.0
Rifabutin	0.3–0.9
Ethambutol	2–6
Amikacin (IV)	C_{max} 3–5 times greater than isolate MAC MIC

[a]Recommended levels from Alsultan and Peloquin.[248]
[b]Measured at 2 h postdose unless specified.
C_{max}, Peak serum concentration; *MAC, Mycobacterium avium* complex; *MIC,* minimal inhibitory concentration.