especially in the elderly population and patients on systemic steroids, and this effect combined with some predilection for causing delirium in older patients, limits its use since these scenarios apply to many patients with MAC disease. The cytopenia-related toxicity with the oxazolidinones can be mitigated without lowering efficacy by using daily dosing instead of the twice-daily dosing used for other bacterial infections, but neuropathy or optic neuritis often is a limiting factor after 4 to 5 months of therapy.[241,242]

Drug Interactions

Neither azithromycin nor ethambutol has significant drug interactions, a major advantage of these agents.[6] Clarithromycin inhibits cytochrome P-450 isoenzyme 3A4 and interferes with the metabolism of drugs that use this isoenzyme, raising their serum levels.[238] Increased serum concentrations of drugs such as carbamazepine, omeprazole, and warfarin may be seen. Serum levels of clarithromycin are also increased when the drug is coadministered with the common drugs fluconazole or ranitidine. Even more importantly, the metabolism of clarithromycin is increased, and thus its serum drug level lowered, when administered with rifamycins.[190,191] In the largest pharmacodynamic study on this topic, the C_{max} of clarithromycin was decreased by 68% compared to a 23% decrease in azithromycin C_{max} with concurrent rifampin administration, leading to peak levels below target range more frequently for clarithromycin (56% vs. 35%).[190] Rifamycins have drug-drug interactions with many medications in addition to macrolides, usually increasing clearance and lowering levels of other drugs by induction of the hepatic microsomal enzyme cytochrome P-450 pathway.[6,190,243] Many drugs can be affected, including clarithromycin, methadone and other opiates, warfarin and almost all other anticoagulants, estrogens, and several classes of HIV antiretrovirals (especially protease inhibitors and non-nucleoside reverse-transcriptase inhibitors).[243,244] When possible, serum levels of these agents should be monitored when coadministered with rifamycins.[243] FQs have a number of drug-drug interactions, and importantly moxifloxacin, the most MAC-active FQ, cannot be used with rifampin due to its metabolism by rifampin causing significantly decreased levels, a problem that does not affect the other FQs.[245] Additionally, there is the possibility of additive QT interval prolongation when FQs and macrolides are used in combination, making consideration of QTc interval monitoring warranted.[6] Coadministration of fluoroquinolones with divalent or trivalent cations (e.g., calcium, ferrous sulfate) can lead to decreased absorption and decreased serum FQ levels, and patients should be counseled to either not take these supplements or separate them by at least 2 to 3 hours from FQ dosing. The primary drug interaction to consider with oxazolidinones is the risk of serotonin syndrome when linezolid is given concurrently with other serotonin-active medications.[246]

Drug Dosing in Impaired Renal Function

Clarithromycin, ethambutol, most FQs, and aminoglycosides are excreted by the kidneys, and doses of these agents should be reduced in patients with renal insufficiency.[6] Rifampin, rifabutin, azithromycin, and the FQ moxifloxacin are excreted largely by the liver and do not require dose reduction when given to patients with renal insufficiency, although consideration should be given to rifamycin dose reduction in end-stage renal disease.[6]

Serum Drug Level Monitoring

The significance of serum levels of the drugs used to treat MAC is largely unclear.[6] Two pharmacologic studies totaling more than 600 persons treated for MAC showed a substantial number of these persons to have serum drug levels below the target range.[190,247] This raises concern for the possibility of monotherapy in certain situations, especially when only two-drug therapy is being utilized. It may also explain suboptimal therapeutic response in some patients.[190,230] Although there are no data clearly correlating serum drug levels or use of drug level monitoring to clinical outcomes, we believe the previously noted findings provide some rationale for drug level monitoring, especially in cases with suboptimal therapeutic response, atypical treatment regimens, complicated drug-drug interactions, or reasons to suspect poor drug absorption.[6] For the first-line MAC agents, serum drug level monitoring should be performed 2 hours after the dose is administered, although sometimes the peak can be delayed in individuals with slowed gastrointestinal absorption.[248] The theoretical goal levels for these drugs largely come from tuberculosis literature, and the application to MAC therapy is still controversial (see Table 251.3).[248] As mentioned previously, when intravenous amikacin is used, therapeutic drug monitoring should always be performed, targeting C_{max}/MIC ratios of 3 to 5.[6]

Macrolide-Resistant *Mycobacterium avium* Complex Disease

Isolates resistant in vitro to clarithromycin are uniformly cross-resistant to azithromycin.[249] There may still be a rationale for continuing the macrolide in treatment of pulmonary MAC disease given immunodulatory benefits, activity against concomitant pathogens, and the possibility of mixed MAC populations (discussed previously). Treatment outcomes for macrolide-resistant disease are generally poor, as discussed earlier. Most experts recommend a four-drug regimen comprising a rifamycin, ethambutol, an FQ (if susceptible) or clofazimine, and an aminoglycoside as initial therapy, although the long-term durability of the aminoglycoside is problematic.[6] Clofazimine in particular has been used with good effect in salvage treatment regimens for MAC, and given this and its more reliably low MICs in vitro than FQs, as well as synergy with the amikacin, which is often used in these cases, clofazimine may be a more optimal agent than FQs in this situation.[250,251] Newer agents for the treatment of tuberculosis, such as linezolid, tedizolid, bedaquiline, and delamanid, have activity against MAC and are probably the best options after quinolones and clofazimine are entertained. The clinical evidence behind these drugs is limited, especially in macrolide-resistant disease, so while their use should be considered, we cannot provide a strong recommendation for their use at this time.[6] When used, linezolid is best dosed as 600 mg daily. Bedaquiline is dosed as 400 mg twice daily for 2 weeks, followed by 200 mg three times weekly.[209,241] Ethionamide and cycloserine can at times have activity but have substantial toxicities that limit their use practically, and they should only be used in consultation with a specialist. Other mycobacterial drugs such as isoniazid and pyrazinamide are minimally active in vitro with no known clinical benefit, although they are still recommended in certain situations by some experts.[17,252]

Immunomodulatory Treatment of *Mycobacterium avium* Complex Disease

MAC disease in patients with inherited immune defects may have a better response to antimycobacterial therapy when treatment to restore or circumvent immune defects is undertaken. When inherited defects in the IFN-γ signaling pathway are present, subcutaneously administered IFN-γ may overcome these defects and may lead to clinical improvement.[253] IFN-γ has not been shown to be of benefit in pulmonary MAC disease without defined immune defects and is not recommended in this setting, although one small and currently unreplicated trial has shown some benefit.[6,254] In patients with either inherited or acquired immunoglobulin deficiencies, there is sometimes a role for intermittent intravenous immunoglobulin replacement to help with disease control, although clinical studies to prove benefit are lacking.

Specific Organ System Treatment Considerations

Pulmonary *Mycobacterium avium* Complex

Treatment Choice and Monitoring

As discussed earlier, the decision to treat for pulmonary MAC is made difficult by the long duration of therapy, drug toxicity, the difficulty of clearing dense infection from areas of bad underlying bronchiectasis or structural lung disease, and the risk of reinfection after effective treatment is completed. Treatment choice is also guided by severity of the pulmonary disease, with more extensive or cavitary disease or both portending a more severe disease state that warrants more intensive treatment (Table 251.4).[6,17,255] In this setting an aminoglycoside, usually intravenous amikacin, should be added three times weekly to the oral backbone regimen for the initial 2 to 4 months of treatment, with specific monitoring as discussed previously.[6,17,207] For the most common disease form, nodular/bronchiectatic disease, the standard regimen involves

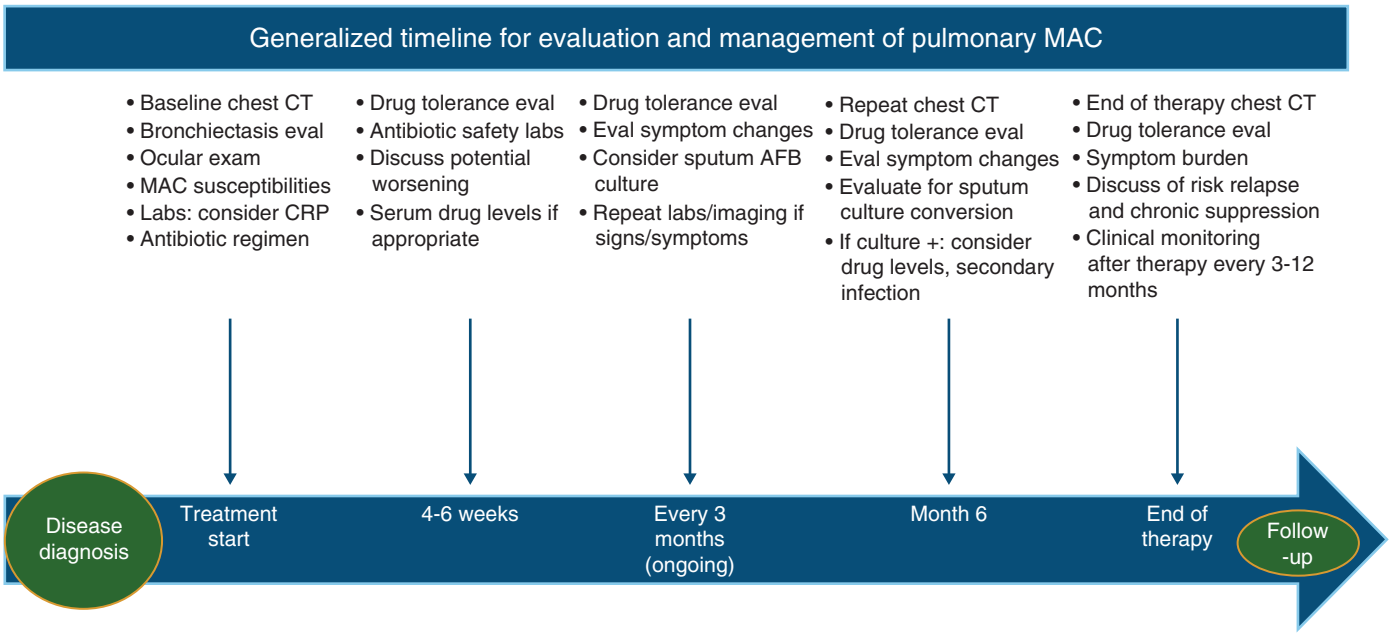

FIG. 251.5 Schematic to guide longitudinal management of individuals with pulmonary *Mycobacterium avium* complex *(MAC)* on therapy. Individual patient characteristics and goals of care should be important considerations in this process. *AFB,* Acid-fast bacilli; *CRP,* C-reactive protein; *CT,* computed tomography; *eval,* evaluation.

TABLE 251.4 Antibiotic Regimens for Disseminated *Mycobacterium avium* Complex

PREFERRED REGIMEN	ALTERNATIVE REGIMEN OR OPTION
Azithromycin 500 mg PO daily *plus*	Clarithromycin 500 mg PO twice daily *plus*
Ethambutol 15 mg/kg PO daily *plus*	Ethambutol 15 mg/kg PO daily *with or without a rifamycin*[b]
Rifampin 10 mg/kg (600 mg max.) PO daily *consider adding*	Rifabutin 300 mg PO daily
Amikacin 10–15 mg/kg IV three times weekly *for the first 4–12 wk*	

[a]See text for full dosing recommendations.
[b]Alterative acceptable regimen: macrolide (azithromycin/clarithromycin) + only ethambutol.
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.*

azithromycin 250 mg daily or clarithromycin 500 mg twice daily, ethambutol 15 mg/kg/day, and rifampin 600 mg daily or rifabutin 300 mg daily, with azithromycin the favored macrolide and rifampin the favored rifamycin for reasons mentioned previously.[6,17] For patients with milder, noncavitary disease, who cannot tolerate the initial regimen, one option is changing from daily to three-times-weekly dosing with dosing adjustments to azithromycin and ethambutol as outlined in Table 251.2.[231,234] This three-times-weekly regimen can also be considered for initial therapy in patients with mild-to-moderate nodular bronchiectatic disease, although the benefits of starting with daily therapy in this setting include more options for deintensifying therapy in response to side effects and, for patients with more advanced noncavitary disease, potentially enhanced efficacy.

We recommend clinical evaluation of the patient every 4 to 6 weeks until stable and then thereafter every 3 to 4 months to evaluate for clinical response, adverse events, and adherence to the drug regimen. Although guidelines suggest treating for 12 months after sputum culture conversion, most patients convert by month 6, and many are not able to produce sputum after the first two or three months.[186,231,234] As a result, while repeating sputum every 1 to 3 months until negative is reasonable to attempt, in the patients in whom it is not feasible, a target treatment duration of 15 to 18 months is appropriate. Shorter durations may be reasonable for patients with minimal disease who show a rapid clinical response to treatment, although data here are limited. In our experience, some patients even have an initial worsening 4 to 12 weeks into treatment due to increased lung inflammation in the setting of mycobacterial death, a clinical situation with faint echoes of the paradoxical response to the initiation of therapy for tuberculosis. As discussed earlier, interval chest radiographs have limited sensitivity for nodular bronchiectatic disease, but we think obtaining chest CT scans roughly 6 months into therapy, at the end of therapy, and at a time of a sustained clinical worsening has utility to guide management. Patients who do not show clinical improvement, whose sputum does not clear of MAC after 6+ months, or who have radiographic worsening after 6 months, should be evaluated for adherence to the regimen, subtherapeutic drug levels, and potential concomitant infections (Fig. 251.5).[6] Although almost all MAC isolates from untreated patients are susceptible to macrolides, resistance can develop during treatment, and since antecedent macrolide exposure is common in individuals with lung disease and resistance to macrolides significantly affects prognosis, macrolide susceptibility testing at the start of therapy is vital.[6,17] As discussed previously, although drug susceptibilities for nonmacrolide antibiotics have never been shown to correlate closely with clinical outcomes, given the less consistent MIC profiles for drugs such as rifamycins, ethambutol, quinolones, aminoglycosides, and linezolid, we recommend this testing at a specialty mycobacterial laboratory before starting therapy and for patients on treatment who remain culture positive after prolonged therapy.

It can be difficult to tell the difference between relapse and reinfection, both of which can occur months or years after treatment, and patients should be followed intermittently after therapy due to this.[6,128,256] When relapse happens, it most commonly happens in the first 9 to 12 months after therapy cessation, while reinfection remains a lifelong risk, especially in those with nodular bronchiectatic disease.[128,256,257] Given the frequency of relapse and reinfection and the difficulty of initial cure, some individuals require either chronic suppressive treatment or intermittent treatment courses throughout life.[6] As mentioned earlier, this dynamic also raises the question of whether "cure" is the appropriate paradigm within which to consider this disease and argues for a more chronic disease management approach focusing on a combination of symptoms, quality of life, and long-term lung function.

Because most individuals with pulmonary MAC disease have either bronchiectasis or other structural lung disease, airway clearance therapies

and other lung disease treatment form an important part of their management.[258,259] Many individuals with milder disease can be managed with aggressive airway clearance/pulmonary hygiene alone and do not require antibiotic therapy.[6,136] Even when antibiotics are necessary, these other interventions should not be forgotten because they are synergistic with antimicrobial therapy.[6,136] Because the physiology predisposing to pulmonary MAC also allows other organisms to gain easier access to the respiratory tree, individuals with MAC disease are usually colonized with and sometimes infected with other pathogens, including other mycobacteria.[129,130,260,261] MAC treatment choice sometimes needs to take these other organisms into account, or clinicians need to consider a superinfection with these other organisms as one of the possible reasons for worsening in a MAC patient.[136,262] *Pseudomonas aeruginosa* in particular is implicated in a more severe disease phenotype in individuals with bronchiectasis, worse quality of life, and exacerbation metrics in pulmonary MAC.[32,129] There is a poorly understood interplay of the lung microbiome here, and in some patients, treatment of MAC sometimes allows other pathogens to flare (and vice versa) as organisms compete for resources within the airway.

Surgery

Surgical lung resection is a possibility for select patients who do not respond to medical therapy or who have focal dense bronchiectatic disease or lung cavities where tissue penetration of antibiotics may be limited.[6] Although some of the surgical procedures for MAC were performed in the pre-macrolide era, surgical resection of MAC-infected lungs continues to be successfully used in the area of macrolide-based regimens.[263–266] Occasionally, patients need surgery to control complications of MAC, such as pneumothorax, severe bronchiectasis, or hemoptysis. Careful patient selection is important because surgery can have significant complications such as pneumothorax, prolonged air leaks, and bronchopulmonary fistulas. Thoracoscopic intervention, although it requires more technical expertise, helps lower the complication rates and should generally be the first-line method of surgical intervention.[264] With careful selection and in experienced surgical hands, outcomes are good, but given the infrequency with which these interventions are performed at most centers, we recommend referral to a center with good experience in the resection of MAC-infected lung tissue.[263–265]

Hypersensitivity Pneumonitis

Most patients with MAC hypersensitivity pneumonitis (hot tub lung) respond to short-term interventions, and some patients are cured simply by avoiding the exposure source.[149,153] When progressive pulmonary symptoms are present, a short (roughly 2 months) course of prednisone with or without antimycobacterial drugs for 3 to 6 months has been shown to be effective, suggesting this is mostly an inflammatory/allergic process and not a deep infection.[153]

Extrapulmonary Disease

Disseminated Disease

For dMAC, antimycobacterial treatment should be initiated promptly for all patients with confirmed disease.[6] In HIV/AIDS patients, empirical treatment is not recommended because clinical suspicion is a poor predictor of dMAC disease, and if pursued the clinician should evaluate for other illness if the cultures remain negative after 6 weeks.[103] All dMAC isolates from patients with HIV/AIDS should have initial susceptibility testing performed because macrolide resistance has been reported to be as high as 15% to 20%.[196] HIV-infected patients should not be treated if they are only colonized with MAC in the sputum or gastrointestinal tract but have no evidence of active infection, although patients should be followed carefully because a high percentage may develop MAC bacteremia within 1 year if effective ART is not instituted.[98] Treatment should involve at least a macrolide (azithromycin 500 mg daily or clarithromycin 500 mg twice daily) and ethambutol dosed at 15 mg/kg/day, although most experts recommend adding a rifamycin as well (see Table 251.4).[201,217] Given that early clinical outcomes are still poor, aminoglycosides are highly effective at more rapidly decreasing disease burden, and that induction with an IV aminoglycoside is usually pursued in severe lung dMAC in the non-HIV population, we recommend considering adding intravenous amikacin for the first 8 to 12 weeks to the above regimen.[217,235,236] Perhaps the most important tenant of therapy for dMAC in HIV/AIDS is the initiation of ART, because patients have improved clinical outcomes and decreased MAC relapse if ART for HIV disease is administered concurrently.[217] ART in this setting should be started as soon as possible.[217] ART can be complicated by drug interactions between the rifamycins and the protease inhibitors and nonnucleoside reverse-transcriptase inhibitors, but in the modern area, anti-HIV integrase inhibitors allow concurrent administration of rifamycins, which is preferred to stopping the rifamycin. Of the integrase inhibitors, raltegravir should be given at double dose of 800 mg twice daily and dolutegravir should be given at a double dose of 50 mg twice daily when administered with rifampin, while neither require dose adjustment when used with rifabutin.[217] It is currently recommended that elvitegravir and bictegravir not be coadministered with either rifampin or rifabutin. When effective antimycobacterial therapy for dMAC in HIV/AIDS patients is instituted, fevers and night sweats usually resolve within 2 to 4 weeks, and mycobacteria are cleared from the blood in 4 to 8 weeks.[217] The response of anorexia, fatigue, and severe anemia can be more variable. Follow-up blood cultures are not necessary for all patients with clinical improvement but should be done for patients who fail to improve after 4 to 8 weeks.[217] MAC isolates from patients failing therapy should be submitted for drug susceptibility testing, although most isolates remain sensitive.[154,200]

The duration of antimycobacterial therapy for dMAC depends on immune status.[6] In HIV/AIDS patients, therapy should be continued indefinitely for those with fewer than 100 $CD4^+$ cells/mm^3, whereas therapy may be discontinued in patients who have received MAC therapy for at least 12 months and have had cell counts of 100 $CD4^+$ cells/mm^3 or greater for at least 6 months.[217] This recommendation is based on several large series of HIV/AIDS patients with dMAC who have had a significant elevation of $CD4^+$ cell counts after starting ART and had antimycobacterial therapy stopped successfully.[267,268] Patients should continue to be followed because there have been occasional reports of patients relapsing with systemic MAC after discontinuation of antibiotics. In general, therapy for dMAC in the non-HIV/AIDS population should follow a similar course. However, since there may not be an immunodeficiency to address with ART, antimycobacterial treatment duration may differ based on clinical response.[6] For situations in which disseminated disease was predisposed by immunosuppressive medications, these should be promptly discontinued or at least the dose should be reduced as much as possible (especially when anti-TNF-α agents or corticosteroids are used).

Some patients beginning ART for HIV/AIDS or withdrawing predisposing immunosuppressive medications experience IRIS, as mentioned previously.[62,111] Most patients with IRIS improve with continuation of therapy.[217] For patients with severe symptoms, a short course (4–8 weeks) of steroids (e.g., prednisone, 0.5 mg/kg daily, tapered as signs and symptoms permit) may relieve symptomatic discomfort, but if the earlier-noted symptoms are persistent or recurrent, workup for additional causes should be undertaken before multiple courses of steroids are administered, although IRIS symptoms can last 3 to 6 months in some cases.[112,217] IRIS can also occur in dMAC in non-HIV/AIDS patients if there was a predisposing immunosuppressive medication that is stopped. In rare situations where this form of IRIS is severe enough, a low dose of the prior immunosuppressive may even have to be reinstituted until symptoms abate.

Prevention. Patients with HIV/AIDS, not on ART, and with $CD4^+$ cell counts of fewer than 50 cells/mm^3 are at high risk of developing dMAC disease, roughly 20% each year.[48,49] Given the high mortality associated with dMAC, primary chemoprophylaxis of MAC can be helpful for patients with $CD4^+$ cell counts below 50 cells/mm^3, with clarithromycin, azithromycin, and rifabutin all showing efficacy and with macrolides more effective in comparison studies.[217,269–272] There does not appear to be added benefit to using combination therapy as prophylaxis. Azithromycin 1200 mg once weekly is the preferred regimen, with azithromycin 600 mg twice a week, clarithromycin 500 mg twice daily, and rifabutin 300 mg daily as alternatives.[217] Before beginning antimycobacterial prophylaxis, patients with symptoms of dMAC should have a mycobacterial blood culture performed to rule out dMAC. Patients on ART whose $CD4^+$ count rises to greater than 100 cells/mm^3 for

greater than 3 months are no longer at increased risk for MAC, and controlled studies have shown the safety of discontinuing prophylaxis in this population.[217,273,274] One more recent change in this field is that, with the introduction of more potent ART, viral load suppression and $CD4^+$ cell count rise to greater than 100 cells/mm^3 happen so quickly that they have often occurred by the time the 6- to 8-week time period at which to document negative AFB blood cultures has elapsed. As a result, there is now a compelling argument against the need for dMAC primary prophylaxis in HIV/AIDS if ART is promptly initiated.[275] In the non-HIV population, there are no immunosuppressive medications at high enough risk for dMAC for primary prophylaxis to be warranted, and this should be avoided in this population.

Other Localized Disease

In the management of MAC lymphadenitis, surgical excision is the treatment of choice.[57,162,276] When complete excision of the node is performed as a diagnostic and therapeutic intervention, concomitant antibiotics are often not required.[276] For individuals for whom surgery poses a high risk, therapy with a macrolide-containing regimen may be successful, although the optimal duration of therapy is unclear.[6,57,277] As mentioned previously, some cases are also self-limited, so intervention is not required in every case.

For skin and soft tissue infection as well as deeper bone and joint infection, optimal therapy usually involves a combination of surgical débridement and antibiotics.[6] There is almost no literature to guide decision making, but we favor induction therapy with two or three oral drugs plus an intravenous aminoglycoside for the first 2 to 4 months, especially in bone and joint disease. Optimal duration of therapy for skin and soft tissue infection is to treat until lesions resolve, usually 4 to 6 months, while in bone and joint infection a duration of 6 to 12 months is probably appropriate, although this should be influenced by adequacy of initial débridement as well as clinical response.[6]

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The complete reference list is available online at Expert Consult.

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252 Infections Caused by Nontuberculous Mycobacteria Other Than *Mycobacterium avium* Complex

Barbara A. Brown-Elliott and Richard J. Wallace, Jr.

SHORT VIEW SUMMARY

DEFINITION

- The category of nontuberculous mycobacteria is composed of species other than *Mycobacterium tuberculosis* complex (MTBC) and *Mycobacterium leprae*. For *Mycobacterium avium* complex, see Chapter 251.
- Previously known as "atypical mycobacteria" or "mycobacteria other than *M. tuberculosis*."
- More than 170 species of nontuberculous mycobacteria (NTM).
- Divided into rapidly, intermediately, and slowly growing species.

EPIDEMIOLOGY

- Most species are worldwide and ubiquitous in the environment, including household water, potting soil, vegetable matter, dust, animals, and birds.
- NTM include pathogens and nonpathogens.
- Cases in chronic pulmonary infections involve patients with underlying disease, such as bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary disease.
- Other cases involve extrapulmonary sites, including skin and soft tissue, bones, joints, bursae, tendon sheaths, lymph nodes, eyes, ears, blood, brain, and cerebrospinal fluid.

MICROBIOLOGY

- Acid-fast bacilli (AFB) stain poorly with Gram staining.
- Identification of definitive species level is only accomplished by molecular or proteomic methods currently.

Rapidly Growing Mycobacteria

- Rapidly growing mycobacteria (RGM) produce mature colonies on solid media within 7 days.
- Routine culture media, such as blood agar, chocolate agar, trypticase soy agar, most MTBC media (Middlebrook 7H10 or 7H11 agar and Lowenstein-Jensen agar), and various broths, including rapid broth detection systems, support the growth of most species.
- Preference is for 28° to 30°C incubation for some species, although many species also grow at 35°C.
- Some RGM, especially *Mycobacterium abscessus,* are adversely affected by decontamination methods that are used for isolation of MTBC.
- Currently, six groups of pathogenic species are defined based on presence or absence of pigment and genetic relatedness.

Intermediately Growing Mycobacteria

- Most MTBC media, including Middlebrook 7H10 or 7H11 agar and Lowenstein-Jensen agar, support growth of species.
- They require 7 to 10 days to reach mature growth.
- Primarily, two pigmented species are involved:
  - *Mycobacterium marinum* (pathogen) grows optimally at 28° to 30°C and is associated with marine water and marine animals.
  - *Mycobacterium gordonae* (nonpathogen) grows optimally at 35° to 37°C and is a common tap water contaminant.

Slowly Growing Mycobacteria

- Produce mature colonies in more than 7 days on solid media.
- Most MTBC media, including Middlebrook 7H10 or 7H11 agar, Lowenstein-Jensen agar, Middlebrook broth, and rapid detection broth systems, support growth of species, except for fastidious species, such as *Mycobacterium haemophilum* (requires hemin or iron) and *Mycobacterium genavense* (requires mycobactin J).
- Most species, except *M. haemophilum* (28°–30°C), *Mycobacterium xenopi* (42°–45°C), and some environmental species, grow optimally at 35° to 37°C.

DIAGNOSIS

Pulmonary

- Signs and symptoms of NTM lung disease are variable and nonspecific.
- Patients often present with chronic cough or throat clearing, with or without sputum production and severe fatigue. Less frequently, malaise, dyspnea, fever, hemoptysis, and weight loss may occur.
- Clinical diagnosis depends on multiple positive microbiologic cultures of respiratory samples for AFB.
- Follow the American Thoracic Society guidelines for diagnosis.
- High-resolution chest computed tomography is useful.
- Routine chest radiographs are recommended.
- Single positive sputum cultures are not definitive for NTM disease.
- Positive bronchoalveolar lavage with known lung (NTM) pathogen considered definitive for NTM disease.
- Expert consultation is required for patients with infrequently encountered or highly drug-resistant species of NTM.

Extrapulmonary

- Infection may involve fever, drainage, bacteremia, granulomatous systemic infections, necrosis, and so forth, depending on the site of infection.
- Clinical diagnosis depends on positive microbiologic smears and cultures for mycobacteria of drainage, biopsy tissue, or body fluid, leading to isolation of specific NTM.

THERAPY

Rapidly Growing Mycobacteria

- *Pulmonary disease*
  - Most pulmonary disease is caused by *M. abscessus* subsp. *abscessus* or *M. abscessus* subsp. *massiliense.*
  - Antimicrobial therapy alone is generally unsuccessful for microbiologic eradication of *M. abscessus* subsp. *abscessus* in the presence of a functional *erm* gene.
  - Drugs used for slowly growing mycobacteria, including MTBC, such as rifampin, rifabutin, ethambutol, isoniazid (INH), streptomycin, and pyrazinamide are not effective.
  - Multidrug regimens of macrolides (azithromycin or clarithromycin), high-dose intravenous (IV) cefoxitin (8–12 g/day in divided doses) or imipenem (1 g twice daily), and low-dose intravenous amikacin (peaks in the 20–25 μg/mL range on once-daily dosing) is probably optimal for adults with *M. abscessus.* Once-daily IV tigecycline is often included; dosage adjustment is usually necessary for clinical improvement, not cure. The role of inhaled routine or liposomal amikacin is not well established.
  - Patients with pulmonary *M. abscessus* subsp. *abscessus* and a functional *erm* gene are treated for several months until clinically improved and may require several courses of treatment.
  - Macrolides may be useful for isolates of *M. abscessus* subsp. *massiliense* but not most *M. abscessus* subsp. *abscessus, Mycobacterium fortuitum,* and *Mycobacterium smegmatis* isolates that contain functional inducible *erm* genes.

SHORT VIEW SUMMARY—cont'd

- Other antimicrobials are often useful for species other than *M. abscessus* and *M. chelonae* (minocycline, doxycycline, trimethoprim-sulfamethoxazole [TMP-SMX], quinolones, linezolid, and, for *M. chelonae,* tobramycin).
- *Extrapulmonary disease*
  - In general, clinicians prescribe a multidrug regimen based on in vitro susceptibility testing, including a macrolide (except in case of isolates with functional *erm* genes).
  - Rifampin, rifabutin, ethambutol, and INH are not effective.
  - Patients with significant disease are treated for 6 months, depending on the severity of infection.
  - Other antimicrobials often useful for species of the *M. fortuitum* group are minocycline, doxycycline, TMP-SMX, quinolones, linezolid, and, for *M. chelonae,* tobramycin.

Intermediately Growing Mycobacteria

- *M. marinum* is found on skin and in soft tissue infections (usually hands).
- Treatment options include macrolides, rifampin, TMP-SMX, or a combination of rifampin and ethambutol.

Slowly Growing Mycobacteria

- *Pulmonary disease*
  - Antibiotic treatment generally follows the regimen for *Mycobacterium avium* complex: rifampin, ethambutol, and a macrolide (clarithromycin or azithromycin) with adjustments depending on in vitro antimicrobial susceptibility testing.
  - Patients are generally treated for 12 months of culture negativity.
- *Extrapulmonary disease*
  - Treatment is the same as for pulmonary disease, except that it is usually for 6 months depending on the severity of infection.

PREVENTION

- Recent suggestion of person-to-person spread of a genotype of *M. abscessus* subsp. *massiliense.*
- Tap (household) water derived from community water systems is considered the major reservoir for most common NTM species.
- Biofilms may render NTM less susceptible to disinfectants and antimicrobials.
- Public health concerns are increasing.

OVERVIEW

The recent advances in mycobacterial culture techniques and the increasing utility of modern molecular techniques for identification of previously unidentified organisms have produced a major resurgence of interest in disease caused by the nontuberculous mycobacteria (NTM). In addition, there has been an increasing appreciation of the defects in lung structure and immune response that predispose to NTM.[1,2] This group of mycobacteria is composed of species other than the *Mycobacterium tuberculosis* complex (MTBC), which consists of *M. tuberculosis, M. africanum, M. bovis, M. canettii, M. caprae* (caprine), and several other lesser known species (*M. pinnipedii, M. microti, M. suricattae* [meerkat], *M. orygis,* and *M. mungi* [mongoose]).[3,4] Although *M. leprae* is not a member of the MTBC, it is usually considered separate from the NTM as it is here (see Chapter 250). Previous names for this group of organisms include "atypical mycobacteria" or "mycobacteria other than *M. tuberculosis*."[5] Currently, there are more than 170 species of NTM, of which more than half are considered to be pathogens or potential sources of human or animal disease. Approximately 20 of these species have been described since 2014.[4,6,7] *Mycobacterium avium* complex (MAC) is described extensively in Chapter 251. By tradition, NTM have been categorized into different groups based on characteristic colony morphology, growth rate, and pigmentation (the Runyon system of classification). This system is now considered outdated as we focus predominantly on rapid molecular systems of diagnostics. However, growth rates and colony pigmentation continue to provide practical means for grouping species of mycobacteria within the laboratory and are thus still useful.[5,7]

Rapidly Growing Mycobacteria

The group of organisms called *rapidly growing mycobacteria* (RGM) includes nonpigmented and pigmented species that produce mature growth on media plates within 7 days. There are currently six groups or complexes of RGM based on pigmentation and genetic relatedness. Nonpigmented pathogenic species within the *M. fortuitum* group now include approximately 10 species: *M. fortuitum, M. peregrinum, M. senegalense,*[4,7–9] *M. setense,*[10] and former members of the third biovariant complex, including *M. septicum,*[11,12] *M. porcinum,*[12] *M. houstonense, M. boenickei, M. brisbanense,* and *M. neworleansense.*[12] A newly described, closely related species, *M. aquaticum,* has been recovered from hemodialysis water but not yet considered pathogenic.[13] In addition, there are six validated species within the second group, the *M. chelonae-abscessus* group (*M. chelonae, M. saopaulense* [a pathogen described in humans and fish],[14] *M. salmoniphilum,*[4] *M. franklinii* [multiple pulmonary and sinus infections],[15,16] *M. immunogenum,*[2] and the recently emended three subspecies of *M. abscessus: M. abscessus* subsp. *bolletii, M. abscessus* subsp. *massiliense,* and *M. abscessus* subsp. *abscessus*, previously designated as *M. bolletii, M. massiliense,* and *M. abscessus,* respectively).[17,18] *M. salmoniphilum* has been revived as a fish pathogen but as yet has not been recovered in human samples.[4] The *M. mucogenicum* group includes three species: *M. mucogenicum* (formerly *M. chelonae*–like organism) and two newer-described species, *M. aubagnense* and *M. phocaicum.*[6,7] A fourth group of pathogenic organisms within the RGM is the *M. smegmatis* group.[7,19] Isolates within this group include two late-pigmenting species: *M. smegmatis* (formerly *M. smegmatis* [sensu stricto]) and *M. goodii.*[7,19] All of these species, including the newly described species, have been recovered from clinical specimens on multiple occasions.[7,19]

The fifth group, (early) pigmenting RGM, contains several species that have been implicated in clinical disease, including *M. flavescens, M. neoaurum, M. vaccae, M. phlei, M. canariasense, M. cosmeticum, M. monacense, M. psychrotolerans,* the thermophilic species *M. thermoresistibile, M. bacteremicum,*[20] and *M. iranicum.*[4] Recent additions include *M. celeriflavum,*[4] *M. hippocampi* (a marine pathogen),[4] and *M. anyangense* (a cattle pathogen).[21] *M. mageritense* (formerly in the *M. fortuitum* group) and *M. wolinskyi* (formerly in the *M. smegmatis* group) have been suggested to comprise a sixth group of nonpigmented species, which are genetically closely related to each other.[7,22,23]

Slowly Growing Mycobacteria

This group includes species of mycobacteria that require more than 7 days to reach mature growth. Some species may also require nutritional supplementation of routine mycobacterial media.[5] The major clinically important established species within this group include the MAC, which is discussed in Chapter 251; *M. kansasii; M. xenopi; M. simiae* complex (*M. simiae, M. lentiflavum*, *M. triplex,* and the newly described pigmented species, *M. europaeum*); *M. szulgai; M. malmoense;* and *M. scrofulaceum.*[4,5] In addition, the *M. terrae–M. nonchromogenicum* complex is now composed of several clinically significant species associated with tenosynovitis, including *M. arupense*[6,24,25]; *M. kumamotonense*[4,5,25]; *M. hiberniae*[2]; *M. heraklionense*[4,24,25]; *M. longobardum*[24]; and most recently, *M. virginiense,*[25] and one pink pigmented species, *M. engbaekii,*[4,24] that, like *M. nonchromogenicum,* has not yet been established as pathogenic.[25] *M. asiaticum,*[26] *M. florentinum,*[6] *M. senuense,*[5] and *M. montefiorense,*[5,6] a pathogen in eels,[5,6] were previously described. Recently described nonpigmented species also include human pathogens and potential pathogens: *M. kyorinense*[4]; *M. noviomagense*[27]; *M. shinjukuense*[4]; *M. sherrisii*[4,6]; *M. koreense*[4]; and *M. riyadhense,*[4] a species related to *M. malmoense* and *M. szulgai,* which was originally identified as MTBC due to a false-positive commercial line probe. Two other species, *M. stomatepiae* and *M. angelicum,* genetically related to *M. szulgai,*[28] have been reported in fish. *M. algericum,*[4] genetically related to the *M. terrae* complex, was described as a pathogen in goats. *M. minnesotense,* described in early 2013, has not been recovered from clinical samples to date.[29] *M. paraterrae, M. paragordonae,* and *M. parakoreense* have rarely been described in patients and still have uncertain clinical significance.[4] Pigmented newly described species include *M. europaeum,*[4]

M. paraseoulense,[4] *M. shigaense,*[4] and *M. parafficum*.[4] *M. persicum*, a pigmented species described in 2017 and related to *M. kansasii,* has been reported in pulmonary samples from four unrelated patients in Iran.[30]

Other previously described pigmented organisms in this group include *M. nebraskense,*[5,6] *M. parascrofulaceum,*[6] *M. parmense,*[6] *M. saskatchewanense,*[6] *M. seoulense,*[6] and *M. pseudoshottsii* (a fish pathogen related to *M. shottsii*).[6]

In Africa and Australia *M. ulcerans* continues to be a major pathogen. Cultivation of this species is difficult because it requires up to several months to grow, so molecular detection and identification are currently more optimal than culture techniques.[26,31,32] Other organisms that require special nutritional supplements include *M. haemophilum,* which requires hemin for growth (hence its name), and *M. genavense,*[26,31–33] which requires mycobactin J and prolonged incubation in broth culture. Most of these slowly growing mycobacteria grow best at 35° to 37°C, with the exception of *M. haemophilum,* which prefers lower temperatures (28°–30°C), and *M. xenopi,* which usually grows well at 42° to 45°C.[26,32,34]

Intermediately Growing Mycobacteria

This group of organisms includes *M. marinum, M. gordonae,* and *M. intermedium*,[2] and a newly described cattle pathogen, *M. bourgelatti*, related to the latter species, may also belong to this group but has not yet been described in humans.[4] These organisms are pigmented and require 7 to 10 days to reach mature growth. *M. marinum* grows optimally at 28° to 30°C, whereas *M. gordonae* prefers 35° to 37°C.[31] *M. intermedium,* an NTM of uncertain clinical significance has an optimal temperature between 31° and 37°C.[2]

Nontuberculous Mycobacteria and the Environment

Most NTM species are readily recovered from the environment. Isolates have been recovered from samples of soil, water, animals, plant material, and birds.[5,23] A few fastidious species that are known to cause disease, such as *M. haemophilum* and *M. ulcerans,* have rarely been recovered from the environment.[32] Although an association with an environmental source may be present, a direct link to the environment has not been proven except for health care–associated disease and pseudooutbreaks. Recently, the possibility of person-to-person spread of a strain of *M. abscessus* subsp. *massiliense* has been reported among patients in a US cystic fibrosis center.[35] Isolates that genetically match the strain have been seen in geographic areas outside the United States, including the United Kingdom and South America.[36–38] Community drinking water systems are considered the major reservoirs for most common human NTM pathogens and thus are of increasing public health interest. Slowly growing NTM species, other than MAC, isolated from household tap water include *M. gordonae, M. kansasii, M. xenopi, M. simiae, M. arupense,* and the newly described *M. aquaticum.*[5,13]

Among the RGM, *M. mucogenicum* and the closely related *M. phocaicum* are common tap water isolates.[7,26] Other RGM species from tap water include *M. porcinum, M. immunogenum,* and *M. chelonae.* Recent studies of household water have shown that biofilms, which are the filmy layers at the solid and liquid interface, are recognized as a source of growth and possibly a mode of transmission for mycobacteria.[5,7,39] Moreover, biofilms may serve to render mycobacteria less susceptible to disinfectants and antimicrobial therapy.[5,39] Biofilms appear to be present in almost all collection and piping systems, so mycobacteria may often be recovered from these sites. The persistence of pathogenic NTM in water and biofilms has important implications in the epidemiology of infections related to water.[5,39]

Nontuberculous Mycobacteria and Clinical Disease

NTM produce six major clinical disease syndromes (Table 252.1), which are reviewed in the following sections.

PULMONARY DISEASE

Geography of Common Nontuberculous Mycobacteria Species

Chronic pulmonary disease in a human immunodeficiency virus (HIV)-negative host is the most common localized clinical disease caused by NTM.[26] In the United States MAC, followed by *M. kansasii,* is the most frequently recognized pathogen.[26] In Canada, some parts of the United Kingdom, and Europe, *M. xenopi* ranks third, whereas *M. malmoense* is second after MAC in Scandinavia and northern Europe.[5,26,32] In southeast England *M. xenopi* and *M. kansasii,* known to be present in local water supplies, are both more common than MAC.[5] A recent study in Ontario, Canada showed that *M. xenopi* was the second most frequently isolated NTM after MAC. The study also revealed that patients with *M. xenopi* disease have higher rates of pulmonary cavitation than MAC and are often associated with chronic obstructive pulmonary disease (COPD) and significant mortality rates.[40] In the United States the third most common cause of NTM pulmonary disease is *M. abscessus* complex, which produces 80% of pulmonary infections caused by RGM.[26] (This study antedated recognition of the subspecies *bolletii* and *massiliense.*) Intriguingly, the proportion of *M. abscessus* subsp. *massiliense* varies geographically.[7,41–43] Reports from Korea and Japan have indicated, inexplicably, that the ratio of *M. abscessus* to all NTM is much higher in South Korea than in other Asian countries, including Japan.[42,43] Reports from the National Institutes of Health in the United States show *M. abscessus* subsp. *massiliense* in 28% of 40 patients with lung disease due to NTM, 21% of 39 isolates in the Netherlands, 22% of 50 patients with cystic fibrosis in France, and 55% of 150 patients and 26% of 102 patients in South Korea and Japan, respectively.[42] Bronchiectasis was found to be significantly more frequent in *M. abscessus* subsp. *abscessus* than in *M. abscessus* subsp. *massiliense.*[42] Recently, *M. abscessus* subsp. *massiliense* has been increasingly recognized in respiratory samples of patients, including patients with cystic fibrosis.[26,44–46] Studies in Korea and Japan and, more recently, the United States (for in vitro MIC studies) have emphasized major differences in macrolide susceptibility patterns and clinical response rates between *M. abscessus* subsp. *abscessus,* of which approximately 80% are resistant to macrolides, and *M. massiliense,* which are usually macrolide susceptible; thus patients with *M. abscessus* subsp. *massiliense* respond favorably to clinical treatment with macrolides, unlike *M. abscessus* subsp. *abscessus.*[7,42,43,47]

Nontuberculous Mycobacteria Species Associated Infrequently With Pulmonary Disease

Among the newly described RGM, pulmonary infection has been reported with *M. iranicum*[4] (from Italy, Iran, and Turkey), the newly validated species *M. franklinii*, and *M. celeriflavum.*[4,15] Less commonly, *M. fortuitum, M. goodii, M. abscessus,* and *M. smegmatis* have been associated with lipoid pneumonia[7,8,19] and achalasia.[7,8,19,26] Patients with achalasia exhibit a bilateral subacute to acute alveolar disease with high fevers, striking leucocytosis count higher than 20,000/μL, cough, and mucus production; acute illness is common. The histopathology shows a combination of lipoid disease and acute/granulomatous infection.[26] Other NTM that are infrequently associated with pulmonary disease include *M. szulgai,*[26,31] *M. simiae,*[26,31] *M. celatum,*[26,31] *M. lentiflavum,*[26,31] *M. asiaticum,*[26,31] *M. heckeshornense,*[26,31] *M. florentinum,*[6] *M. arupense,*[6,26] *M. kumamotense,*[4,25] *M. nebraskense,*[4,26] and rarely, *M. gordonae,*[26,31] *M. saskatchewanense,*[6,31] *M. senuense,*[31] and *M. seoulense.*[4] Recently described species *M. kyorinense,*[4] *M. noviomagense,*[4] *M. paraseoulense,*[4] *M. europaeum,*[4] (recently validated, but not recently described), *M. shinjukuense,*[4] *M. koreense,*[48] *M. sherrisii,*[2,4] and the aforementioned new species in the *M. terrae* complex[4,24] have also been associated with pulmonary disease. Some isolates originally described as *M. nonchromogenicum* and thought to be pathogenic have recently been identified as *M. heraklionense.*[4] Rarely, isolates of *M. persicum,*[30] *M. parakoreense,*[4] *M. paraense,*[49] and *M. talmoniae*[50] have also been recovered from pulmonary samples.

Pulmonary Syndromes Associated With Nontuberculous Mycobacteria Other Than *Mycobacterium avium* Complex

Clinical disease with *M. kansasii* produces upper lobe fibrocavitary disease and nodular disease similar to MAC in the same setting. The *M. abscessus* complex also produces nodular disease in the setting of bronchiectasis. Pulmonary NTM disease is rare in children, except for those with cystic fibrosis.[26,44] *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* have been increasingly recovered from respiratory samples collected from patients with cystic fibrosis.[41] The

TABLE 252.1 Major Clinical Syndromes Associated With Nontuberculous Mycobacterial Infection Other Than *Mycobacterium avium* Complex

SYNDROME	MOST COMMON CAUSES (OTHER THAN MAC)	LESS FREQUENT CAUSES
Chronic nodular lung disease (adults with bronchiectasis; cystic fibrosis)	*M. xenopi, M. malmoense, M. kansasii, M. abscessus* subsp. *abscessus, M. abscessus* subsp. *massiliense, M. abscessus* subsp. *bolletii*	*M. szulgai, M. smegmatis, M. celatum, M. simiae, M. goodii, M. asiaticum, M. heckeshornense, M. branderi, M. lentiflavum, M. triplex, M. fortuitum, M. abscessus* subsp. *bolletii, M. florentinum, M. nebraskense, M. saskatchewanense, M. seoulense, M. senuense, M. paraseoulense, M. europaeum, M. algericum* (goats), *M. sherrisii, M. kyorinense, M. noviomagense, M. celeriflavum, M. franklinii, M. fragae, M. insubricum, M. iranicum, M. llatzerense, M. shinjukuense, M. koreense, M. heraklionense, M. parascrofulaceum, M. parakoreense, M. paraense, M. persicum, M. talmoniae*
Cavitary lung disease	*M. abscessus* subsp. *abscessus*	*M. europaeum, M. riyadhense, M. xenopi*
Cervical or other lymphadenitis (especially children)	*M. malmoense* (northern Europe), *M. lentiflavum,*	*M. scrofulaceum* (rarely), *M. abscessus, M. fortuitum, M. tusciae, M. palustre, M. interjectum, M. elephantis, M. heidelbergense, M. parmense, M. bohemicum, M. haemophilum, M. europaeum, M. florentinum, M. triplex, M. asiaticum, M. kansasii, M. heckeshornense, M. bourgelatii* (cattle)
Skin and soft tissue disease	*M. fortuitum* group, *M. chelonae, M. abscessus, M. marinum, M. ulcerans* (Australia, tropical countries only)	*M. kansasii, M. haemophilum, M. porcinum, M. smegmatis, M. genavense, M. lacus, M. novocastrense, M. houstonense, M. goodii, M. immunogenum, M. mageritense, M. abscessus* subsp. *massiliense, M. monacense, M. bohemicum, M. branderi, M. shigaense, M. szulgai, M. asiaticum, M. xenopi, M. kumamotense, M. setense, M. montefiorense* (eels), *M. pseudoshottsii* (fish), *M. salmoniphilum* (salmonids), *M. shottsii* (fish), *M. hippocampi* (sea horses), *M. iranicum, M. llatzerense*
Skeletal (bone, joint, tendon) infection	*M. marinum, M. fortuitum* group, *M. abscessus, M. chelonae*	*M. haemophilum, M. heckeshornense, M. smegmatis, M. wolinskyi, M. goodii, M. lactus, M. triplex, M. xenopi M. terrae* complex *(M. arupense, M. heraklionense, M. kumamotense, M. longobardum, M. virginiense)*
Disseminated infection		
HIV-seropositive host	*M. kansasii,*	*M. marinum, M. simiae, M. fortuitum, M. conspicuum, M. celatum, M. lentiflavum, M. triplex, M. sherrisii, M. heckeshornense, M. genavense, M. haemophilum, M. xenopi*
HIV-seronegative host	*M. abscessus, M. chelonae*	*M. marinum, M. kansasii, M. haemophilum, M. xenopi M. conspicuum, M. shottsii* (fish), *M. pseudoshottsii* (fish)
Catheter-related infections	*M. fortuitum, M. abscessus, M. chelonae*	*M. mucogenicum, M. phocaicum, M. immunogenum, M. mageritense, M. septicum, M. porcinum, M. bacteremicum, M. brumae, M. neoaurum*
Hypersensitivity pneumonitis	Metal workers Hot tub	*M. immunogenum*

HIV, Human immunodeficiency virus; *MAC, Mycobacterium avium* complex.
Too little information is available for selected pathogens such as *M. xenopi, M. malmoense, M. szulgai, M. celatum,* and *M. asiaticum* and the newly described species. The role of *M. scrofulaceum* is unclear. With the advent of newer molecular identification methods, the numbers of this species have decreased.

majority of patients with the *M. abscessus* complex are younger and have more severe disease.[44] Patients with cystic fibrosis also have bronchiectasis in addition to chronic recurrent airway and parenchymal infections that may predispose them to NTM infections.[44]

Clinical Presentation of Nontuberculous Mycobacterial Lung Disease

Because the signs and symptoms of NTM lung disease are often variable and nonspecific, disease with NTM is difficult to diagnose without positive respiratory cultures (Table 252.2).[26] Patients often present with chronic cough, a "throat clearing" with or without sputum production, and fatigue. Less frequently, complaints of malaise, dyspnea, fever, hemoptysis, and weight loss may also be present. Clinical studies should include microbiologic cultures for acid-fast bacilli (AFB) and routine chest radiographs. High-resolution chest computed tomography (CT) is essential in patients suspected of having nodular bronchiectasis. Recovery of NTM from a single sputum sample is not proof of NTM disease, especially when the AFB smear is negative and NTM are present in low numbers.[26,51] The American Thoracic Society statement on the diagnosis and treatment of NTM[26] has revised the diagnostic criteria to determine lung disease caused by NTM (Table 252.3).[26] For NTM disease due to organisms other than MAC, these criteria may need to be adjusted because inadequate data are available to evaluate these criteria. Expert consultation should be obtained when NTM that are infrequently encountered are recovered.[26]

Treatment of *Mycobacterium avium* Complex Lung Disease

This issue is discussed separately in Chapter 251.

Treatment of *Mycobacterium kansasii* Lung Disease

Treatment of lung disease caused by *M. kansasii* has traditionally been less difficult than that for MAC since the introduction of rifampin.[26] A regimen of daily rifampin, 600 mg, isoniazid (INH), 300 mg, and ethambutol, 15 mg/kg, has been widely accepted in the United States and is still recommended by the American Thoracic Society (Table 252.4).[26,45] In HIV-positive patients receiving a protease inhibitor or nonnucleoside reverse-transcriptase inhibitor, rifampin should be replaced by rifabutin, although the dosage depends on the antiretrovirals. The rifabutin dose should be decreased to 150 mg daily in patients receiving amprenavir, atazanavir, nelfinavir, and ritonavir. Rifabutin should be increased to 450 mg daily or 600 mg thrice weekly in patients receiving efavirenz. Maraviroc dose should be doubled if it must be used with rifabutin. Patients taking elvitegravir-cobicistat-tenofovir-emtricitabine should not be given rifabutin. No rifabutin dose adjustment is required for patients taking raltegravir, nevirapine, or etravirine.

TABLE 252.2 Clinical Settings for Nontuberculous Mycobacterial Lung Disease (Other Than *Mycobacterium avium* Complex)

RADIOGRAPHIC DISEASE	SETTING	USUAL PATHOGEN[a] (RARE PATHOGEN)
Upper lobe cavitary	Male smokers, often abusing alcohol, usually early 50s	*M. kansasii*
Right middle lobe, lingular nodular bronchiectasis	Female nonsmokers, usually older than 60 yr	*M. abscessus, M. abscessus* subsp. *massiliense (M. kansasii)*
Localized alveolar, cavitary disease	Prior granulomatous disease (usually tuberculosis) with bronchiectasis	*M. abscessus*
Reticulonodular or alveolar bilateral lower lobe disease	Achalasia, chronic vomiting secondary to gastrointestinal disease, exogenous lipoid pneumonia (mineral oil aspirations, etc.)	*M. fortuitum (M. abscessus, M. smegmatis, M. goodii)*
Reticulonodular disease	Adolescents with cystic fibrosis, HIV-positive hosts, may be prior bronchiectasis secondary to *Pneumocystis* pneumonia or other cause	*M. abscessus* subsp. *abscessus,*[b] *M. abscessus* subsp. *massiliense*
Hypersensitivity pneumonitis	Metal workers Indoor hot tub	*M. immunogenum*

[a]Too little information is available for selected pathogens such as *M. xenopi, M. malmoense, M. szulgai, M. celatum,* and *M. asiaticum* and the newly described species.
[b]If a functional *erm* gene is present, treatment with clarithromycin may not be warranted.
HIV, Human immunodeficiency virus.

TABLE 252.3 American Thoracic Society Diagnostic Criteria for NTM Lung Disease

The minimum evaluation of a patient for NTM lung disease should include:
1. Chest radiograph or, when no cavitation is present, HRCT
2. At least three sputum or respiratory samples for AFB culture
3. Exclusion of other disease such as tuberculosis

Clinical diagnosis of NTM is based on pulmonary symptoms, presence of nodules or cavities as seen on chest radiograph or an HRCT scan with multifocal bronchiectasis with multiple small nodules, and exclusion of other diagnoses.

Microbiologic diagnosis of NTM:

At least two expectorated sputa (or at least one bronchial wash or lavage) with positive cultures for NTM or transbronchial or other lung biopsy showing the presence of granulomatous inflammation or AFB with one or more sputum or bronchial washings that are culture positive for NTM.

AFB, Acid-fast bacilli; *HRCT,* high-resolution computed tomography; *NTM,* nontuberculous mycobacteria.
Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. American Thoracic Society Statement. Am J Respir Crit Care Med. *2007;175:367–416.*

Patients should be treated with at least 12 months of culture negativity.[26] For patients resistant or intolerant to rifampin, clarithromycin is a reasonable alternative agent.[26,45,52]

The usefulness of INH in this regimen is controversial, with a macrolide offering a much better alternative. In the United Kingdom INH is omitted from the regimen. A recent study in Japan showed little difference in the addition of INH in a small number ($n = 14$) of patients.[53] An intermittent regimen (three times weekly) using clarithromycin in place of INH (the same drugs and drug concentration as for MAC) suggests that intermittent therapy for *M. kansasii* can be highly effective, although it has been reported only in a limited number of patients.[52] This regimen is currently preferred by some experts.[26,52]

Untreated strains of *M. kansasii* are susceptible to low concentrations of rifampin, rifabutin, ethambutol (although in vitro susceptibility results [MICs] may appear resistant due to technical difficulties with testing ethambutol), linezolid, streptomycin, sulfonamides, clarithromycin, and the quinolones. Information on the clinical utility of drugs other than rifampin or ethambutol is limited.[26,52] Acquired mutational resistance of *M. kansasii* to rifampin can occur, but this organism is readily treated with multidrug regimens.[26,52]

Treatment of *Mycobacterium abscessus* subsp. *abscessus* and *Mycobacterium abscessus* subsp. *massiliense* Lung Disease

Treatment of *M. abscessus* (with a functional *erm* gene, which inactivates the macrolides) lung disease with antimicrobials alone has generally been unsuccessful.[26,45] Courses of therapy in adults with clarithromycin, high-dose IV cefoxitin (8–12 g/day in two to three divided doses) or imipenem (1 g twice daily), and low-dose parenteral amikacin (peaks in the 20- to 25-μg/mL range on once-daily dosing) produce clinical improvement with limited toxicity but usually do not result in microbiologic cure.[7,26] Studies using an IV glycylcycline antibiotic, tigecycline, have shown good in vitro activity (minimal inhibitory concentrations [MICs], ≤1 μg/mL) against most species of clinically important RGM, including the *M. abscessus* complex,[54,55] and this drug is now often included in multidrug therapy, especially in patients who have developed amikacin auditory toxicity. A recent clinical trial reported successful treatment of three patients with *M. abscessus* lung disease using amikacin liposome inhalation suspension (ALIS).[56] However, no data are available to compare ALIS with nonliposomal administration, and further large studies are needed to assess the effectiveness of this new agent.[57] Inhaled commercial (IV) amikacin has also been used but with limited reported results.[56] There are preliminary data that bedaquiline may be useful in *M. abscessus* infection, but large clinical trials and in vitro MIC studies are needed.[58]

A concern for the usefulness of the macrolides for *M. smegmatis, M. fortuitum*, and the *M. abscessus* subsp. *abscessus* is that the majority of these species, including approximately 80% of the isolates of *M. abscessus* subsp. *abscessus*, contain functional inducible *erm* genes (*erm38, erm39,* and *erm41*, respectively), which induce macrolide resistance and are likely responsible for treatment failure in macrolide-containing regimens against the *M. abscessus* complex other than *M. abscessus* subsp. *massiliense*.[47] In addition to inducible macrolide resistance, acquired macrolide resistance due to mutations in the 23S ribosomal RNA (rRNA) gene can develop during antibiotic treatment.[59]

Isolates of *M. abscessus* subsp. *massiliense* and approximately 15% of subsp. *abscessus* isolates do not contain functional *erm* genes and hence are intrinsically macrolide susceptible. These isolates usually show good clinical response to clarithromycin-containing regimens, with response rates up to 85%.[47,60–66]

Treatment of Other Nontuberculous Mycobacterial Lung Disease

A recommended or standardized treatment for lung disease caused by other slowly growing mycobacteria, such as *M. simiae, M. szulgai, M. xenopi, M. malmoense,* and the newly described species, has not been established.[26,45] Drug combinations similar to those used with MAC, such as clarithromycin, ethambutol, rifabutin, and perhaps an aminoglycoside with 12 months of negative cultures, seem reasonable.[26,32,34,45]

Pseudooutbreaks of pulmonary disease have been described, usually related to contamination of bronchoscopes or the automated endoscope washing machine.[26,39] *M. immunogenum* is the most common species recovered in this setting, followed by *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense*.[7,39] *M. immunogenum* has also been associated with hypersensitivity pneumonitis associated with occupational exposure to metalworking fluids.[67]

LYMPHADENITIS

Localized cervical lymphadenitis is the most common NTM disease in children, with a peak incidence between 1 and 5 years of age.[26] NTM-affected lymph nodes are usually in the anterior cervical chain

TABLE 252.4 Frequently Used Treatment Regimens for Common Nontuberculous Mycobacterial Pathogens Other Than *Mycobacterium avium* Complex

SPECIES	DISEASE[a]	DRUG	DAILY ADULT DOSES[b]	THREE TIMES WEEKLY ADULT DOSE	DURATION
M. kansasii	Pulmonary				
	(United States)	Isoniazid *or*	300 mg	—	Culture negative at least 12 mo
		Clarithromycin *plus*	500 mg bid	500 mg bid	
		Rifampin *plus*	600 mg	600 mg	
		Ethambutol	15 mg/kg	25 mg/kg	
	(United Kingdom)	Rifampin *plus*	600 mg	600 mg	9–12 mo
		Ethambutol	15 mg/kg	15 mg/kg	
	Disseminated	Same as pulmonary			
	HIV-positive	Same as pulmonary (United States) but replace rifampin (rifampin inactivates HIV drugs) with rifabutin *or*	150 mg		Same as pulmonary (United States)
		Clarithromycin[c]	500 mg bid		
M. abscessus subsp. *abscessus* (80% of isolates harbor functional *erm* gene)	Pulmonary (adults)	Amikacin IV (peaks in low 20s μg/mL)	7.5–10 mg/kg single dose daily[d]	NA	2 wk (designed to improve, not cure)
			500 mg daily inhaled amikacin or ALIS		ALIS: not determined
M. abscessus subsp. *massiliense* (no functional *erm* gene)		*Plus* imipenem IV *or*	1 g bid		
		Cefoxitin IV *or*	8–12 g/day (divided into 2–3 doses)		2 wk
		Tigecycline 25–50 mg IV once daily			
		Plus clarithromycin[e]	500 mg bid		6 mo
	Cutaneous localized	Clarithromycin	500 mg bid[f]		6 mo
	Disseminated or extensive cutaneous	Same three drugs as above[g]		NA	Not established
M. marinum	Cutaneous	Clarithromycin *or*	500 mg bid	NA	3 mo minimum for all regimens
		Minocycline *or*	100 mg bid		
		Rifampin *plus*	600 mg		
		Ethambutol	15 mg/kg		

[a]HIV-negative host unless otherwise stated.
[b]Drugs by mouth unless otherwise stated.
[c]Patients on HIV medicines inactivated by rifampin.
[d]Based on age, weight, and renal status (American Thoracic Society).
[e]If a functional *erm* gene is present, treatment with clarithromycin may not be warranted.
[f]Patients with complicated lesions may require surgical débridement and amikacin plus cefoxitin or imipenem.
[g]Amikacin plus clarithromycin plus imipenem or cefoxitin or tigecycline.
ALIS, Amikacin liposome inhalation suspension; *bid,* twice daily; *HIV,* human immunodeficiency virus; *IV,* intravenous; *NA,* not applicable.

and are unilateral and painless. The nodes may enlarge rapidly with the formation of fistulas to the skin, and prolonged drainage may occur. On occasion, other nodes outside the head and neck, such as the mediastinal lymph nodes, may be involved.[5,26] A definitive diagnosis of NTM lymphadenitis is made by recovery of the etiologic organism from lymph node cultures. The tuberculin skin test is often weakly positive (5–10 mm), but it may be more than 10 mm.[26] Routine biopsy or incision and drainage should be avoided because these procedures often result in the formation of fistulas and chronic drainage. Fine-needle aspiration with cytology and culture has been used increasingly with apparently few associated problems.

The Italian Society of Preventive and Social Pediatrics has recently proposed a practice algorithm using a multidisciplinary approach to define categories of patients, including those to "watch/wait," those requiring empirical antibiotic therapy, and those needing prompt diagnostic workup, considering the risk for severe underlying disease for the management of pediatric cervical lymphadenopathy.[68]

Treatment of NTM cervical lymphadenitis is still evolving. The potential role of macrolide treatment regimens without surgery or as a supplement to surgery in complicated or recurrent disease is being considered with increasing frequency. Clarithromycin combined with ethambutol or rifabutin is the usual suggested regimen (see Table 252.4). However, the established treatment of routine NTM cervical lymphadenitis (from the premacrolide era) remains surgical excision without antimicrobial treatment.[26]

Since the early 1980s, 80% of cases of culture-positive NTM lymphadenitis in children in the United States have been caused by MAC.[5,26] The remainder of the cases in Australia and the United States were caused by *M. scrofulaceum,* and only about 10% of the cases have been caused by *M. tuberculosis*.[5,26] The incidence of *M. scrofulaceum* has declined since the 1980s and is now a rare cause of the lymphadenitis. Although not yet described in lymph node culture, some isolates that were previously identified as *M. scrofulaceum* by phenotypic methods have been found to be a genetic match for *M. parascrofulaceum,* suggesting that the prevalence of this new species may have previously been underestimated. In parts of northern Europe, including Scandinavia and the United Kingdom, *M. malmoense* has become the second most common pathogen after MAC.[5,26,32,69] *M. lentiflavum* appears to be an increasing cause of cervical lymphadenitis in selected geographic areas.[5,70] The same is true for *M. haemophilum* because a recent report from Israel showed that the rate of isolation of *M. haemophilum* in cervical lymphadenitis since 1996 has been 51%.[32] Rarely, other species are recovered, including RGM,[5,8,26] *M. heckeshornense, M. asiaticum, M. florentinum, M. kansasii, M. interjectum, M. parmense, M. palustre, M. tusciae, M. heidelbergense, M. elephantis, M. triplex, M. bohemicum,* and *M. europaeum*.[2,5,6] For cases that fail to grow NTM, DNA sequencing has emerged as a means to provide an etiology in these cases.[71]

A report from Thailand of 128 HIV-negative adult patients described disseminated NTM infection with bilateral lymphadenitis in 89% of the patients. The majority of infections were caused by RGM, including *M. abscessus, M. fortuitum, M. chelonae,* and *M. thermoresistibile.* Unlike the more common form of NTM lymphadenitis in children, all but 1 of 129 patients were adults whose infection spread to other organ involvement.[72] Subsequent studies revealed these patients to have acquired autoantibodies to interferon-γ. In addition, a rare case of systemic *M. abscessus* complex (no subspecies identification was provided) lymphadenitis in a Japanese patient with leukemia was recently published.[73]

LOCALIZED CUTANEOUS, JOINT, AND SOFT TISSUE INFECTIONS

Although most pathogenic species of NTM have been incriminated in cutaneous NTM disease, the most common etiologic agents are *M. marinum, M. ulcerans,* and the RGM.[7,8,26,45,74]

Intermediately Growing Mycobacteria

Mycobacterium marinum

M. marinum causes an infection historically recognized as "swimming pool" or "fish tank" granuloma.[26,45,74] This common name is derived from the epidemiologic niche of the organism. Most infections occur 2 to 3 weeks after contact with contaminated water from one of these sources. The lesions are most often small violet papules on the hands and arms that may progress to shallow, crusty ulcerations and scar formation. Lesions are usually singular. However, multiple ascending lesions resembling sporotrichosis ("sporotrichoid disease") can occasionally occur.[26,74] Most patients are clinically healthy, with a previous local hand injury that becomes infected while cleaning a fish tank, or patients may sustain scratches or puncture wounds from saltwater fish, shrimp, fins, and other marine life contaminated with *M. marinum*. Swimming pools seem to be a risk only when nonchlorinated. Diagnosis is made from culture and histologic examination of biopsy material, along with a compatible history of exposure. No treatment of choice is recognized for *M. marinum* (see Table 252.3). However, successful treatments have traditionally been a two-drug combination of rifampin plus ethambutol or monotherapy with doxycycline, minocycline, clarithromycin, or trimethoprim-sulfamethoxazole (TMP-SMX) given for a minimum of 3 months. Clarithromycin has been used increasingly because of good clinical efficacy and minimal side effects, although published experience is limited.[26,45,74]

Community-Acquired Extrapulmonary Infections Due to Rapidly Growing Mycobacteria

The rapidly growing species *M. abscessus, M. fortuitum*, and *M. chelonae* are the most common NTM involved in cases of community-acquired infections of skin and soft tissue in the United States.[7,8,26,45] The *M. fortuitum* group is responsible for 60% of localized cutaneous infections in previously healthy individuals. Unlike infections with the *M. chelonae–M. abscessus* complex, the patient with *M. fortuitum* localized infection usually has no predisposing immune suppression.[5,7,45] In a series of 42 patients for whom clinical history was available, the majority of infections involved some type of traumatic injury, such as metal puncture wounds from stepping on a nail (48%), motor vehicle accidents (26%), and injuries involving the foot or leg (≈40%).[5,7,45] Open lacerations or fractures were common. *M. setense,* a newer member of the *M. fortuitum* group, has been described in a case of osteomyelitis.[10]

In contrast, localized infections with *M. chelonae* are seen primarily in patients who are immunosuppressed, especially on long-term corticosteroids. Autoimmune diseases, such as rheumatoid arthritis and systemic lupus, are often predisposing factors.[7] In a study by Wallace and colleagues,[8,26,45] 35% of the *M. chelonae* with nonpulmonary infections were seen in localized wound infections.

Disease due to the *M. abscessus* complex occurs in normal hosts and those with immune suppression. Examples of localized wound infection with *M. abscessus* include soft tissue infection of the cheek after an insect bite and vertebral osteomyelitis.[7,26]

Since 2002 several outbreaks of lower-extremity folliculitis due to RGM (*M. fortuitum, M. abscessus,* and *M. mageritense* disease), associated with nail salons ("foot-spa disease"), have been reported.[5,7,39] Leg hair removal by wax stripping, followed by NTM-contaminated foot baths has resulted in indolent folliculitis.

Recent outbreaks of RGM infections, especially with *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* after cosmetic surgeries and mesotherapy, have also been described.[7,39,75]

Slowly Growing Mycobacteria

On occasion, localized community-acquired infections of the skin, soft tissue, synovium, or bone may involve slowly growing species, such as MAC, *M. szulgai, M. xenopi, M. asiaticum,* and *M. kansasii*. Rarely, species such as *M. novocastrense, M. lacus, M. branderi, M. bohemicum,* and *M. monacense* are involved.[4,26] Among the newer described species, *M. shigaense* has been recovered from skin biopsies of both immunocompromised and immunocompetent patients.[4] Hand infections involving tendons and/or joints (tenosynovitis) has long been associated with *M. terrae* complex. Recent sequencing studies have shown the major species in this group causing tenosynovitis are *M. arupense, M. kumamotonense, M. heraklionense,* and the newly described species *M. virginiense,* but not *M. nonchromogenicum,* as was previously thought.[25]

Health Care–Associated Infections

Sporadic cases of health care–associated skin and soft tissue disease have also been described. These cases include infections of long-term intravenous (IV) or peritoneal catheters; postinjection abscesses; surgical wound infections, such as after cardiac bypass surgery; and augmentation mammoplasty and cosmetic procedures, including tattooing.[26,39,45] Infections after insertion of prosthetic devices, including prosthetic heart valves and joints, have also been reported.[76]

A cluster of 12 cases involving *M. fortuitum* and *M. porcinum* in postaugmentation mammoplasty surgical site infections was recently described in Brazil.[5,7,39] Clustered outbreaks or pseudooutbreaks of mycobacterial skin, soft tissue, or bone infections have been described and usually result from contaminated fluids, such as ice made from tap water, irrigation, exposure to tap water, injectable medicines, and topical skin solutions/markers.[5,7,26,39]

The contamination of benzalkonium chloride (a quaternary ammonium commonly used as an antiseptic) with *M. abscessus* was responsible for a serious outbreak of *M. abscessus* after steroid injections and serves to emphasize the limitations of disinfectants against mycobacteria, especially quaternary ammonium compounds ("quats").[7,39] There have been reports of eye disease due to RGM, including postkeratoplasty and after laser-assisted in situ keratomileusis (LASIK) surgery for correction of myopia.[8,77] A cluster of *M. chelonae* keratitis was associated with hyperopic LASIK using a contact lens mask. Thirty-one of 43 additional cases of keratitis between 2000 and 2001 were part of this outbreak, whereas the 12 other reported cases were sporadic.[5,77]

Other outbreaks involving NTM have involved contamination of liposuction equipment with *M. chelonae,* with the same disease strain found in tap water used for rinsing suction tubing.[39] Most of the skin and soft tissue disease outbreaks have involved the rapidly growing species *M. fortuitum* and *M. abscessus*.[7,8,39,75] However, an outbreak of disease in four patients with alcohol-resistant mycobacterial species (two with *M. chelonae* and two with *M. nonchromogenicum*) was reported in Hong Kong after acupuncture treatments from 1999 to 2000.[39] In addition, between 2003 and 2004, an outbreak of *M. abscessus* occurred in patients from the United States who visited the Dominican Republic for cosmetic surgery for fat removal (known as "lipotourism").[7,39] In 2013 21 patients were found to have NTM wound infections after cosmetic surgery in the Dominican Republic.[7,78] Thirteen were at a single clinic, and all except one of the cultures were *M. abscessus* complex. The average time postoperatively for swelling and pain to develop was 3 weeks. Although no water samples or environmental samples were available for testing in either outbreak, the reservoir for these types of outbreaks has historically been municipal or hospital water supplies.[39]

Outbreaks of species including *M. cosmeticum* and *M. abscessus* subsp. *massiliense* have also been described recently from postinjection abscess after influenza or cold antibiotic injections, cosmetic procedures, and laparoscopic surgeries in Korea, Brazil, Venezuela, and Ohio.[18,39,75,79,80] Of major concern, a single strain of *M. abscessus* subsp. *massiliense* was incriminated in an epidemic of surgical site infections in Brazil since 2004.[81] This strain has been the subject of several reports. Additional outbreaks have involved *M. haemophilum* and *M. chelonae* in patients who received tattoos.[7,39,82]

Recently, a large outbreak of hospital-associated *M. abscessus* was reported in the United States. Approximately one-half of the cases were lung transplant patients with respiratory cultures positive for *M. abscessus*. Elimination of tap water exposure among high-risk patients decreased the incidence rate to baseline numbers. The investigation also noted that one-half of the cases occurred in cardiac surgery patients with invasive infections. Intense disinfection protocols and use of sterile

water for heater-cooler units of cardiac bypass machines, along with specific engineering strategies, mitigated the outbreak.[83]

SKIN/SOFT TISSUE

Diagnosis and Treatment

Diagnosis of all types of mycobacterial skin and soft tissue infections is made by culture of specific NTM from drainage material or tissue biopsy. Treatment may include amikacin, cefoxitin, ciprofloxacin, moxifloxacin, clarithromycin, doxycycline, linezolid, sulfonamides, and imipenem for the *M. fortuitum* group. Only amikacin, cefoxitin, tigecycline, imipenem, and sometimes linezolid and clarithromycin have activity against *M. abscessus*. Only amikacin, imipenem, tigecycline, tobramycin, clarithromycin, and sometimes linezolid, moxifloxacin, and doxycycline have activity against *M. chelonae*.[7,8,26,45] Approximately 25% of strains of *M. chelonae* also show susceptibility to doxycycline and quinolones, including moxifloxacin.[7] Clarithromycin is generally the drug of choice for localized disease (but not for disseminated disease) caused by *M. chelonae* and macrolide-susceptible isolates of *M. abscessus*.[7,26,45] However, the efficacy of macrolide treatment for the majority of *M. abscessus* subsp. *abscessus* (and the *M. fortuitum* group) is likely diminished by recent recognition that they harbor functional *erm* genes that confer inducible resistance to macrolides.[45,47,60–63] The duration of therapy is usually 4 to 6 months.

Antituberculous agents, other than ethambutol for *M. smegmatis,* have no efficacy against any of the RGM and should not be used.[7,26,45,84] Monotherapy with quinolones is not recommended because of the high risk of mutational resistance of RGM to these agents. Treatment of slowly growing species is similar to that for chronic lung disease, except that the duration of therapy may only be 6 to 12 months, depending on the severity of the disease.[26,45]

Two unusual species causing skin and soft tissue infections in select situations are *M. ulcerans* and *M. haemophilum*. *M. ulcerans* is not endemic in the United States, but it is endemic in northern areas of Australia and tropical locations of the world, where it is commonly known as the "Buruli ulcer."[26,32,85] *M. ulcerans* is extremely slow growing, with the average incubation time around 8 to 12 weeks, and *M. haemophilum* may take up to 3 to 4 weeks to grow on primary culture.[26,32,45,84] Thus newer molecular techniques for identification of these organisms have expedited diagnosis of infection with the organisms.[26,45] The *M. ulcerans* infection progresses from an itchy nodule, most often on the extremities, to a necrotic lesion that may result in severe limb deformity. Treatment success is common in early disease with excisional surgery. Regimens have included streptomycin and dapsone with or without ethambutol and combinations of rifampin, sulfonamides, ethambutol, and clarithromycin. However, for advanced ulcerative disease, therapeutic response has generally been poor.[26,45] Surgical débridement and skin grafting then become the usual therapeutic measures of choice.[26,45] *M. haemophilum* causes cutaneous infections (primarily of the extremities) in immunosuppressed patients, especially in the setting of organ transplantation, long-term high-dose steroid use, or HIV.[26,31,32,45] The majority of cases involve skin and soft tissue infections.[32] *M. haemophilum* has a special growth requirement for hemin or iron and may present some diagnostic difficulties if iron- or hemin-supplemented media and lower temperatures (incubation at 28°–30°C) are not used.[26,32,45] A surprising number of specimens are AFB smear positive and culture negative, so a presumptive diagnosis is often based on typical caseating granulomas and a negative culture for *M. tuberculosis* in the common clinical setting. Therapy for this species usually includes combinations of clarithromycin and rifampin or rifabutin for 12 to 24 months. The addition of granulocyte-macrophage colony-stimulating factor with reduction of immunosuppression therapy has been associated with a successful outcome in a cardiac transplant patient.[5,26,32,45] Of note, *M. montefiorense* and *M. pseudoshottsii,* as well as *M. stomatepiae,* have been recovered from granulomatous lesions in eels and fish, respectively.[2]

INFECTION OF TENDON SHEATHS, BONES, BURSAE, AND JOINTS

Both rapidly growing and slowly growing species of NTM have been implicated in chronic granulomatous infections involving tendon sheaths, bursae, bones, and joints after direct inoculation of the pathogen through accidental trauma, surgical incisions, puncture wounds, or injections.[8,26,45,86] Most patients have no underlying immune suppression, but high risk for some pathogens, such as *M. chelonae, M. haemophilum,* and *M. xenopi,* is seen in patients who are immunosuppressed.[26,32,39,45] *M. marinum* and *M. heckeshornense* have been described as causing tenosynovitis of the hand,[26,45] although the RGM, *M. kansasii,* and *M. terrae* complex (especially *M. arupense*, *M. heraklionense*, and *M. virginiense*) have also been associated with a chronic type of disease.[5,24–26,45,87,88] Osteomyelitis of the sternum caused by *M. fortuitum* and *M. abscessus* has also been found in clustered outbreaks and sporadic cases after cardiac surgery.[7,26,39,83] Other species—*M. goodii, M. wolinskyi, M. porcinum,* and *M. setense*—have been isolated from posttraumatic osteitis and osteomyelitis. In addition, *M. haemophilum* has a tendency to involve bones and joints, usually with concurrent draining skin lesions and bacteremia.[31,32,45] A newly described species, *M. decipiens,*[86,89] has also been associated with tenosynovitis. *M. lacus* has been recovered from infected synovial fluid.[2] Recently, an outbreak of 58 cases of bone and joint infections in immunocompetent patients in a French hospital involved *M. xenopi*.[39]

Management of mycobacterial rheumatologic infections often requires surgical débridement for both diagnosis and therapy, especially for the closed spaces of the hand and the wrist and for patients with infected bones, such as fractured long bones or the sternum after cardiac surgery. Drug therapy for the specific pathogen is also essential.[5,26]

DISSEMINATED DISEASE

In the setting of advanced HIV infection, most disseminated NTM disease is due to *M. avium.* However, other NTM, including *M. kansasii, M. genavense, M. haemophilum, M. simiae, M. celatum, M. malmoense, M. marinum,* and RGM, have also been recovered.[8,26,32] Disseminated disease among *M. triplex, M. lentiflavum, M. heckeshornense*, *M. conspicuum,* and *M. sherrisii* has also been reported.[22,26,31,32]

After MAC, disseminated *M. kansasii* is the second most frequent cause of disseminated NTM disease in the setting of acquired immunodeficiency syndrome.[26,90] Pulmonary and cutaneous manifestations have occurred[26,90] in patients with chronic lymphocytic leukemia, after organ transplantation, and in those infected by HIV. One study reported five patients with disseminated *M. kansasii* infection, including three patients with pulmonary and extrapulmonary involvement and two patients with exclusive extrapulmonary involvement. All patients had $CD4^+$ lymphocyte counts less than 200 cells/μL. The most common clinical manifestation was pulmonary disease with thin-walled cavitary lesions.[5,26] Before the advent of antiretroviral therapy, *M. genavense* was the second most frequently isolated species after *M. avium* in some geographic areas.

Disseminated disease in non-HIV patients has been reported and is most frequently caused by *M. chelonae.*[7] Disseminated disease involving *M. chelonae* is primarily cutaneous and typically presents as a chronic syndrome with multiple painful, draining, red nodules, usually involving the lower extremities.[5,7,26] Almost all patients are immunosuppressed, usually from corticosteroid therapy for disease such as rheumatoid arthritis. Other types of immune suppression occur in patients with autoimmune disease, leukemia, or transplanted organs. Although the disease is presumably a consequence of hematogenous spread, a portal of entry is rarely evident, and septicemia is rare.[7,26,45]

Although the majority of disseminated cutaneous disease is due to *M. chelonae, M. abscessus* complex has been reported in approximately 20% of the cases. Disease involving sites other than the skin is rare, except in severely immunosuppressed patients. Disseminated disease with *M. abscessus* is a serious disease and can be difficult to treat.[5,26,45,73] Other NTM, such as *M. haemophilum,* produce similar clinical syndromes in similar settings with infection, most often in the lower extremities in immunosuppressed patients.[26,32]

CATHETER-RELATED INFECTIONS

Currently, catheter-related infections are the most common health care–associated NTM infections encountered.[7,8,20,26] Infections are seen most often with long-term central IV catheters, but they may also occur with peritoneal or shunt catheters. The usual pathogens are RGM, especially *M. fortuitum* and *M. mucogenicum* (see Table 252.1). These infections may be manifested as fever, local catheter site drainage, bacteremia, or, occasionally, lung infiltrates or granulomatous hepatitis. The usual treatment is catheter removal combined with appropriate antibiotics for 6 to 12 weeks.[5,7,26,91]

An outbreak of *M. phocaicum,* a member of the *M. mucogenicum* group, was reported in central venous catheters in an oncology unit of a Texas hospital.[5,39,45] Isolates of the RGM species *M. neoaurum, M. brumae, M. mageritense,* and the recently described *M. bacteremicum* have also been incriminated in catheter-related sepsis.[2,20,22]

MISCELLANEOUS INFECTIONS

Less commonly, NTM have been associated with other types of infections, including central nervous system (CNS) and ocular infections.[26,44,77,92] NTM, including *M. genavense, M. kansasii, M. malmoense,* and RGM, primarily *M. fortuitum,* have been identified with CNS disease.[26,45,92] The first known case of *M. abscessus* meningitis was described in 2001 in a 59-year-old woman who had no significant medical history but had sustained a knife wound to the neck months before her symptoms.[92]

Recently, the newly described *M. iranicum*[93] and *M. doricum*[2] were recovered from cerebrospinal fluid cultures of patients, although the latter species was considered of uncertain significance.

Ocular infections have most often involved the RGM, especially the *M. abscessus–M. chelonae* group.[26,45,77] The number of infections has increased to include postkeratoplasty and post-LASIK surgery. As previously discussed, infections have been associated with outbreaks and in sporadic fashion.[26,77] Treatment for patients with corneal infections due to RGM is usually complicated by the lack of available effective antimicrobials.[26,77] For patients who do not respond to topical antimicrobials, surgical interventions are recommended.[45,77]

RGM can cause mastoiditis and chronic otitis media of insidious onset, usually in children with a perforation or ventilation tube in the tympanic membrane.[5] Infection appears with ear drainage or polyps in the external auditory canal. CT shows opacification of the mastoid air cells, with or without destruction of bony septae. Mastoidectomy tissue is full of granulomas, but AFB are not seen. Cultures of the mastoid tissue grow RGM, usually *M. abscessus* complex. Treatment involves surgical removal of infected tissue and months of antimycobacterial treatment.

LABORATORY ASPECTS

Stain and Culture

The methods used for staining and culture of *M. tuberculosis* generally work well for the NTM, although the yield of some NTM, especially the RGM, may be adversely affected by the decontamination methods that are standard for *M. tuberculosis*.[26,33,51] Middlebrook 7H10 or 7H11 agar and the rapid broth systems all support growth of the commonly encountered NTM.[26,51,84] Cultures of skin and soft tissue should be plated at 28° to 30°C, as well as at 35°C, because species such as *M. marinum, M. chelonae,* and *M. haemophilum* grow only at low temperatures on primary isolation.[23,26,31] *M. genavense* (broth for 6–8 weeks)[5,26,31,45] and *M. haemophilum* (iron or heme in the media and lower temperatures)[5,26,32] have special growth requirements.[5,26,31,45,94] If *M. ulcerans, M. genavense,* or *M. malmoense* is suspected, cultures should be held up 10 to 12 weeks before discarding.[26,32] Due to the difficulty often encountered in growing *M. ulcerans* and *M. genavense* on solid media, molecular techniques are usually necessary to identify these species directly from broth.[5,26,32,33]

Identification

Identification of NTM increasingly focuses and depends on the use of rapid diagnostic systems. High-performance liquid chromatography, which assesses the patterns of long-chain fatty acids (mycolic acids) has generally been replaced by molecular methods such as gene sequencing of multiple genes, including 16S rRNA, *hsp65*, *rpoB,*[4,6,26,95] and commercially available molecular probes. The latter probes for RNA are currently available for *M. tuberculosis*, *M. avium, M. intracellulare,* MAC, *M. gordonae,* and *M. kansasii*.[5,26] For most of the newer species, partial gene sequencing of the 16S rRNA gene, *rpoB* gene, or both, are important or essential for species identification.[2,4,6,26] Molecular methods, including the INNO-LiPA multiplex probe assay has been introduced into the United States. This assay targets the 16S-23S internal transcribed spacer (Innogenetics; Ghent, Belgium), whereas the GenoType *Mycobacterium* assay targets the 23S rRNA gene (Hain Lifescience; Nehren, Germany). These two methods have been widely used in Europe for identification of multiple species of NTM.[2,4,31,96]

Other methods of identification include pyrosequencing, a short sequence analysis method based on detection of pyrophosphate during DNA synthesis,[31,97] and mass spectral identification by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).[4,7] To date, MALDI-TOF has reliably identified some species of NTM but not the rarer species.[98] Moreover, it cannot differentiate the closely related members of the *M. fortuitum* group and the subspecies of the *M. abscessus* complex. The efficacy of this method greatly depends upon the availability of quality updated databases.[33] Thus further study of this technique is warranted.

Biochemical testing to determine carbohydrate use is slow and inadequate and should be replaced by molecular methods for more definitive identification.[4,7] It should also be emphasized that NTM species identification obtained before the use of modern molecular techniques should be suspect until identification is confirmed by molecular methods.[4,7]

Susceptibility Testing: Rapidly Growing Mycobacteria

The three most widely used methods of susceptibility testing of RGM include agar disk elution, broth microdilution, and the E-test gradient MIC.[26,45,84] In 2003 the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards) published a document for global standardization of susceptibility testing of mycobacterial species, including the NTM.[23,45,84] The only CLSI-recommended method for susceptibility testing with RGM is the broth microdilution technique.[45,84] Antituberculous agents are not effective against these species. The document was revised in 2011 to include recommendations for moxifloxacin, meropenem, and detection of the inducible *erm* gene in RGM.[84] Testing of tigecycline has not been addressed by the CLSI, yet, although it appears to be a useful antimicrobial against most RGM.[55] There are no recommended mycobacterial breakpoints.[7,54,84] Minimal recommendations for testing the RGM include clarithromycin (used as a class representative agent for the new macrolides), amikacin, cefoxitin, imipenem, doxycycline, linezolid, ciprofloxacin, TMP-SMX, and tobramycin (for *M. chelonae* only).[26,84]

Susceptibility Testing: Slowly Growing Nontuberculous Mycobacteria

The proportion method in agar, broth microdilution, E-test, and automated broth systems, including the MGIT (mycobacteria growth indicator tube) (Becton, Dickinson and Company; Franklin Lake, NJ) and the VersaTrek/ESP (Thermofisher, formerly Trek Diagnostics; Cleveland, OH) techniques, have been used for determining MICs of the slowly growing NTM.[45,84] However, only the broth microdilution susceptibility testing is currently recommended by the CLSI for all slowly growing species.[45,84] Susceptibility testing of rifampin and clarithromycin (used as the class agent for the macrolides, including azithromycin), rifabutin, minocycline, amikacin, linezolid, quinolones (ciprofloxacin and moxifloxacin), and TMP-SMX for most slowly growing NTM species (other than MAC) is recommended.[5,45,84] Ethambutol MICs are not reproducible and MIC results may be misleading, potentially unnecessarily eliminating an effective agent from the treatment regimen.[84] Susceptibility testing to pyrazinamide is not recommended because it has no efficacy against NTM. Currently, susceptibility testing to rifampin and clarithromycin only is recommended for isolates of *M. kansasii.* Isolates of *M. kansasii* that are resistant to rifampin should be tested against the aforementioned panel of antimicrobials.[84] Isolates of *M. kansasii* that are susceptible to rifampin will also be susceptible to rifabutin and should require no additional testing.[26,45,84]

If considered clinically significant, isolates of slowly growing NTM (other than MAC) should be tested against all of the aforementioned drugs.[5,26,45,84] Streptomycin and INH may be useful clinically, but the CLSI has not addressed breakpoints for these antimicrobials.[26,45,84]

Isolates of *M. marinum* may not require susceptibility testing unless the patient fails to respond to treatment after several months.[26,45,84] However, recent resistance trends among isolates of this species may necessitate more frequent testing.

The role of antimicrobial susceptibility testing for some NTM remains uncertain.[99] With the increasing clinical significance of NTM disease, further testing, especially of the newly described species, is warranted.

Strain Comparison

Molecular methods, such as random amplified polymorphic DNA polymerase chain reaction (RAPD), pulsed-field gel electrophoresis (PFGE), repetitive sequence-based PCR (rep-PCR), multilocus sequence typing (MLST), and more recently, whole-genomic sequencing (WGS) have been used for strain comparison, ("DNA fingerprinting") of NTM (non-MAC) outbreaks.[26,31,39,41,100] PFGE has been the most widely used technique applicable to essentially all species of NTM and has been considered the gold standard for definitive strain comparison of the NTM. With recent modifications to the technique to eliminate DNA degradation, strain typing is feasible for all species of mycobacteria.[100,101] Variable number tandem repeat (VNTR) has been useful in some outbreak studies of *M. abscessus*,[83] whereas the potential of WGS, especially core genomics, remains largely untapped among many NTM species. Genomic sequencing may potentially not only aid in the identification of species but can potentially identify genetic determinants that characterize species diversity and strain specificity that may provide insight into the aspects of environmental survival, antibiotic resistance, and ultimately the pathogenicity of strains or species. Although WGS is generally not widely available in clinical and reference laboratories, it is emerging as an important tool in the study of NTM.[102,103]

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The complete reference list is available online at Expert Consult.

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