Diagnosis and Treatment of Infections due to *Mycobacterium avium* Complex

Shannon H. Kasperbauer, M.D.[1] and Charles L. Daley, M.D.[1]

ABSTRACT

Mycobacterium avium complex (MAC) consists of nontuberculous mycobacteria that cause disease in immunocompromised and immunocompetent hosts. The organisms are ubiquitous in the environment, and acquisition occurs through ingestion or inhalation of aerosols from soil, water, or biofilms. Disease may manifest as disseminated infection, soft tissue infection, chronic pneumonia, or hypersensitivity pneumonitis. Nontuberculous mycobacteria are increasingly associated with pulmonary disease, with MAC being the most common nontuberculous mycobacteria to cause pulmonary disease in the United States. Pulmonary symptoms, nodular or cavitary opacities on a chest radiograph or high-resolution computed tomographic scan with multifocal bronchiectasis and multiple small nodules, plus positive culture results from two sputum specimens or one bronchoscopic specimen are consistent with MAC pulmonary disease. Treatment consists of a macrolide, rifamycin, and ethambutol given three times weekly for noncavitary disease and daily with or without an aminoglycoside for cavitary disease.

KEYWORDS: *Mycobacterium avium* complex, nontuberculous mycobacteria, diagnosis, treatment

Mycobacterium avium complex (MAC) includes at least two species, *Mycobacterium avium* and *Mycobacterium intracellulare*. Recent molecular studies have documented that *M. avium* is composed of several subspecies and that the one most likely to cause disease in humans is subspecies *hominissuis* (Table 1).[1] These organisms belong to a much larger group of bacteria referred to as nontuberculous mycobacteria (NTM), environmental mycobacteria, atypical mycobacteria, or mycobacteria other than tuberculosis. Disease manifests as chronic pneumonia; disseminated infection; skin, soft tissue, and bone infection; and acute hypersensitivity pneumonitis.

Unlike tuberculosis, MAC is not transmitted from person to person. It is ubiquitous in the environment; thus one likely acquires it from various exposures to the environment. Organisms are present in soil, water, biofilms, and aerosols. MAC is resistant to disinfectants used in water treatment centers and can thus be isolated from drinking water.[2]

EPIDEMIOLOGY

Studying the incidence and prevalence of disease due to NTM is challenging for many reasons. NTM infections are not reportable, specimen contamination can confound results, and determining infection from disease relies on additional clinical insight. In a review of the epidemiology of nontuberculous pulmonary disease, the infection rate in North America was estimated to be 1.0 to 12.0 per 100,000 persons, whereas disease rates were 0.1 to 2.0 per 100,000 persons.[3] Ten different studies from the 1960s through the 1990s were analyzed in the review. The report defined infection as isolation of viable

[1]Division of Mycobacterial and Respiratory Infections, National Jewish Health, Denver, Colorado.

Address for correspondence and reprint requests: Shannon H. Kasperbauer, M.D., Division of Mycobacterial and Respiratory Infections, National Jewish Health, 1400 Jackson St., Denver, CO 80206 (e-mail: kasperbauers@njc.org).

Tuberculosis; Guest Editor, Neil W. Schluger, M.D.

Semin Respir Crit Care Med 2008;29:569–576.
DOI 10.1055/s-0028-1085708. ISSN 1069-3424.

Table 1 Nomenclature for *Mycobacterium avium* Complex (MAC) Organisms

Name of Organism	Characteristics
Mycobacterium avium	
M. avium subsp. *avium*	Causes avian tuberculosis. The organism is distinct from the subspecies that causes disease in humans (see below).
M. avium subsp. *hominissuis*	Causes disease in humans and pigs and is frequently isolated from the environment. The organism is the primary cause of disseminated disease in patients with AIDS.
M. avium subsp. *paratuberculosis*	Causes Johne's disease, which is a chronic granulomatous enteric disease of livestock and wildlife. The organism has been postulated to cause Crohn's disease in humans.
Mycobacterium intracellulare	Causes pulmonary disease in both immunocompetent and immunosuppressed patients. The organism is often isolated in the environment.

organisms from an uncontaminated clinical specimen in the absence of obvious clinical manifestations, and disease as the addition of signs or symptoms that suggest a pathogenic process. Because the prevalence of pulmonary infection due to NTM in the United States appeared to be rising, it was unclear whether this was due to better detection of the disease or an actual increase in the amount of infection. To answer this question, Khan et al reviewed data on *M. intracellulare* sensitization in 1971–72 and compared this to rates from 1999–2000. The prevalence of *M. intracellulare* sensitization increased from 11.2% (95% confidence interval, 9.2 to 13.5%) to 16.6% (95% confidence interval, 13.2 to 20.6%). Increasing sensitization to *M. intracellulare* antigens over time supports the theory that infection rates are actually increasing.[4] Marras et al studied the isolation prevalence of pulmonary NTM in Ontario from 1997–2003: 22,247 pulmonary isolates were obtained from 10,231 patients. The isolation prevalence of all species (excluding *Mycobacterium gordonae*) was 9.1/100,000 in 1997, increasing to 14.1/100,000 by 2003 ($p < 0.0001$). This was a mean annual increase of 8.4%.[5] Of note, the rate of tuberculosis was decreasing during the study period.

PULMONARY DISEASE

MAC is the most frequent cause of pulmonary infection due to an NTM in the United States. Pulmonary disease due to MAC manifests as a chronic lung infection, with radiographic changes including bronchiectasis, nodules, and/or cavitary lesions. Patients with isolated pulmonary disease due to MAC are typically immunocompetent adults. Traditionally patients have been described with two types of clinical disease: (1) men with underlying lung disease who present with apical fibrocavitary disease (Fig. 1) and (2) postmenopausal women who present with nodular opacities and bronchiectasis typically in the right middle lobe and lingula (Fig. 2).[6] Investigation for underlying etiologies of bronchiectasis is warranted because further progression of bronchiectasis will only make it more difficult to treat the infection. Screening for genetic, immunologic, rheumatologic, and mechanical

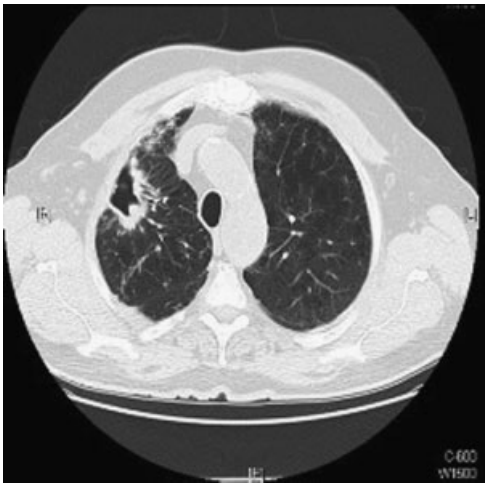

Figure 1 Chest computed tomographic scan. Right upper lobe cavitary opacities in 63-year-old man with *Mycobacterium avium* complex infection and underlying emphysema.

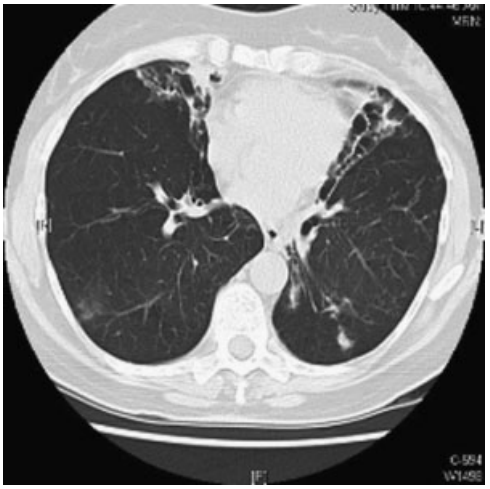

Figure 2 Chest computed tomographic scan. Lingular and right middle lobe bronchiectasis with scattered nodules in a 50-year-old woman with *Mycobacterium avium* complex infection.

Table 2 Clinical and Microbiological Criteria for Diagnosing Nontuberculous Mycobacterial Lung Disease[6]

Clinical Criteria	Microbiological Criteria
Pulmonary symptoms OR	Positive culture results from at least two separate expectorated sputum samples OR
Nodular or cavitary opacities on chest radiograph OR	Positive culture results from at least one bronchial wash or lavage OR
HRCT with multifocal bronchiectasis with multiple small nodules	Lung biopsy with mycobacterial histopathologic features and a positive culture for NTM from the biopsy OR
AND	Lung biopsy with mycobacterial histopathologic features and one or more sputum or bronchial washings that are culture positive for NTM
Appropriate exclusion of other diagnoses	

HRCT, high-resolution computed tomography; NTM, nontuberculous mycobacteria.

causes has revealed that a significant degree of this patient population has an undiagnosed etiology associated with the bronchiectasis.[7]

The American Thoracic Society and the Infectious Disease Society of America released the latest guidelines for the diagnosis and treatment of NTM in 2007.[6] When compared with the previous statement published in 1998 there were a few changes made to the diagnostic criteria. The diagnosis of pulmonary MAC is based on clinical, microbiological, and radiographic criteria (Table 2). The minimum evaluation of a patient with suspected pulmonary disease due to mycobacteria should include a chest radiograph or a high-resolution computed tomographic scan (HRCT) in the case of noncavitary disease, and three or more sputum specimens for acid-fast bacilli (AFB) analysis. Isolation of the bacteria on a single sputum culture is not sufficient for a diagnosis of pulmonary MAC because the organisms exists naturally in the environment.

Treatment of Pulmonary *Mycobacterium avium* Complex

A HISTORICAL PERSPECTIVE

Treatment for MAC can be thought of in three distinct eras, that in which rifampin and ethambutol were not used, that in the premacrolide era in which rifampin and/or ethambutol were used, and that which occurs now in the macrolide era. Field et al[8] published a comprehensive review of all of the treatment studies for MAC lung disease. The reported ranges of success varied from 20 to 90% in the individual studies from the premacrolide era. When an intention to treat strategy was applied the estimated overall cure rate was 40%. Twelve studies were included in the macrolide era. Including treatment dropouts and relapses, the cure rate was ~56%. Overall treatment outcomes have improved with the addition of macrolides to the standard regimen. Thus far, the macrolide class is the only antibiotic for which in vitro susceptibility has been shown to correlate with clinical response to treatment (Table 3).

A prospective, multicentered trial took place in France in the 1990s to assess treatment outcomes in patients with pulmonary MAC with clarithromycin alone or in combination with other antimycobacterial agents. Of the 42 patients enrolled, seven either failed to convert their cultures at 12 months or experienced a relapse. Of these seven cases, susceptibilities of MAC strains isolated from sputum before and after 3 months of treatment were compared, and a significant increase of clarithromycin MIC was observed (0.5 to 2 mg/L to 512 mg/L), indicating an acquired resistance of *M. avium* strains to clarithromycin in five cases.[9]

In a later prospective, noncomparative trial patients received initial clarithromycin monotherapy for 4 months or until their sputum cultures converted to negative.[10] Twenty patients completed 4 months of clarithromycin at 500 mg twice daily. Ninety-five percent (19/20) were found to have pretreatment isolates that were macrolide susceptible. Fifty-eight percent of these patients became sputum-culture negative, whereas an additional 21% of patients had a significant reduction in their sputum positivity. Unfortunately, three of the 19 patients developed macrolide resistance from exposure to monotherapy, which was associated with clinical and microbiological relapse.

Table 3 Outcomes of Clinical Trials for the Treatment of Pulmonary MAC

	Studies	Sample Size	Culture Conversion	Success
Regimens	*N*	Range (mean) *N*	Range (mean) (%)	Range (mean) (%)
No ethambutol or rifampin	7	15–116 (47)	25–65 (38)	20–46 (32)
Ethambutol and/or rifampin	18	14–123 (57)	19–81 (51)	18–64 (38)
Macrolide-containing	12	10–103 (43)	28–84 (63)	26–71 (56)

At the same center, the authors initiated a noncomparative trial of initial azithromycin use in patients with pulmonary MAC. Of 29 patients enrolled, 23 completed therapy. Thirty-eight percent met the primary end point of culture negativity, whereas two patients (9%) were later found to have developed macrolide resistance.[11]

The relationship between clinical efficacy of treatment regimens and drug susceptibility was also examined in Japan by Kobashi et al.[12] Fifty-two patients with pulmonary MAC were enrolled in a prospective study. MICs of rifampin, ethambutol, streptomycin, and clarithromycin were obtained on each isolate. The only consistent relationship between clinical efficacy and susceptibility was with clarithromycin. However, the doses of the other drugs used in the study were too low to allow definitive conclusions regarding clinical efficacy and in vitro susceptibility results.

A multicentered observational study from Japan enrolled 65 patients able to complete 24 months of antibiotics and had at least 12 months of follow-up.[13] The treatment consisted of rifampin 450 mg/day, ethambutol 400 mg/day, clarithromycin (either 400 mg/day for weight < 50 kg, or 600 mg/day for a weight > 50 kg), and streptomycin 1 g/ thrice weekly for the first 2 to 3 months. They noted the sputum conversion rate was significantly lower in patients infected with clarithromycin-resistant strains (0%) and intermediate strains (29%) than in those infected with susceptible strains (66%, $p < 0.05$). Clinical improvement was also significantly lower in patients with clarithromycin-resistant strains (0%) and intermediate strains (14%) than in those infected with susceptible strains (37%; $p < 0.05$). The degree of lung involvement also correlated with outcomes. Patients with more advanced disease beyond the unilateral lung field had significantly higher sputum relapse rates and significantly lower clinical improvement. Finally, a significant difference in sputum conversion was demonstrated in 600 mg/day of clarithromycin versus 400 mg/day of clarithromycin (67.6% vs 42.9%, $p < 0.05$).

As clearly demonstrated macrolide resistance confers worse outcomes. Apart from macrolide monotherapy the risk factors for the development of resistance are less clear.

The minimum inhibitory concentrations (MICs) to 283 strains of *M. avium* were determined by Kuwabara and Tsuchiya.[14] They found 1/243 isolates from untreated individuals to be macrolide susceptible versus 17/40 (43%) patients who had received prior macrolide chemotherapy. All 17 had been treated with clarithromycin monotherapy. Interestingly 8/23 patients who were susceptible to clarithromycin had also been treated with clarithromycin monotherapy. Many of the resistant isolates exposed to monotherapy were classified as the nonnodular bronchiectasis type, suggesting that cavitary disease is another risk factor for the development of macrolide resistance in the face of monotherapy.

Griffith et al went on to further characterize patients with macrolide resistance.[15] Of 51 patients included in the study, 27 were of the upper lobe cavitary phenotype and 24 were the nodular/bronchiectatic phenotype. Initial macrolide monotherapy, a macrolide plus a quinolone, or either of these occurring as a result of discontinuation of ethambutol were the major reasons for development of macrolide resistance.

One explanation for the combination of a macrolide and flouroquinolone leading to macrolide resistance is examined in a study by Kohno et al.[16] They evaluated the in vitro and in vivo activities of three fluoroquinolones and clarithromycin against clinically isolated MAC strains using a mouse model. Clarithromycin showed the best anti-MAC activity in vivo. When the combinations of fluoroquinolones and clarithromycin were studied in vitro 53 to 57% of the isolates exhibited antagonism measured in a fractional inhibitory concentration index (FIC). In vivo studies noted that most of the fluoroquinolone–clarithromycin combinations did not show a significant difference in antibacterial effects in organs compared with treatment with clarithromycin alone. However, several combinations (e.g., moxifloxacin–clarithromycin and gatifloxacin–clarithromycin against MAC strain N084) showed significantly greater numbers of viable bacteria in organs than treatment with clarithromycin alone. This suggests that the antagonism seen with the fluoroquinolone–clarithromycin combinations may be strain dependent.

Recently developed fluoroquinolones, including the C-8 methoxy group, have antimycobacterial activity. For patients who have failed prior treatment or have developed resistance the class holds promise as an alternative agent. Although we do not clearly understand the relationship of flouroquinolone in vitro susceptibility testing to in vivo response, we reported recently the overall susceptibility to fluoroquinolones in MAC to be low. Four hundred and eighteen MAC isolates were examined for their in vitro susceptibility to ciprofloxacin versus moxifloxacin; the percent susceptible were 9 and 13%, respectively.[16a]

Treatment of pulmonary MAC is expensive and has been associated with significant drug intolerance. In an attempt to reduce drug intolerance investigators reported the use of three times weekly (tiw) for the treatment of pulmonary MAC disease. In three studies evaluating the use of azithromcyin-based regimens, the authors reported that 55 to 65% of patients converted their culture to negative with 12 months of negative cultures.[17] Failure to convert cultures to negative after 6 months of therapy occurred in 35 to 45% of patients. In a short term study of intermittent clarithromycin, 78% of patients had converted their cultures to negative by 6 months of therapy, a proportion that was not

significantly different from previous studies that used daily clarithromycin or intermittent azithromycin-based regimens.[18]

Treatment outcomes of tiw therapy were described in a study that was designed to evaluate the impact of inhaled interferon-gamma in the treatment of moderate to severe pulmonary MAC disease.[19] The study was halted because of no documented activity of interferon. However, the outcomes of the patients, all of whom received tiw therapy, were reported. Only 44% of the patients converted their sputum cultures to negative; however, this ranged from 71% in persons with noncavitary disease to 20% in those with cavities present on a chest radiograph. Factors associated with culture conversion included having noncavitary disease, being AFB smear negative, no history of previous treatment, older age, and longer duration of ethambutol use.

CURRENT TREATMENT RECOMMENDATIONS

Based on the studies just described, the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) published guidelines for the treatment of MAC and other NTM.[6] In treatment-naive patients, therapy for pulmonary disease due to MAC includes three oral antimicrobials: a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). For initial therapy of nodular/bronchiectatic disease, tiw therapy is recommended (Table 4). Daily therapy is recommended for initial treatment for cavitary disease. Some experts would also recommend intravenous or intramuscular amikacin or streptomycin for the initial first 2 to 3 months in patients with cavitary disease.[6] Duration of treatment is for 12 months beyond the time that the patient's cultures convert to negative, which usually equates to 18 to 24 months of therapy. Referral should be considered in patients who have failed therapy or are intolerant of a standard treatment regimen. Surgery should be considered in patients who have focal cavitary disease, underlying macrolide resistance or who are failing treatment. The procedure should be performed by surgeons with experience in this type of lung resection and in collaboration with a physician or team with experience in managing these difficult-to-treat patients.

PUBLICATIONS SINCE RELEASE OF THE AMERICAN THORACIC SOCIETY GUIDELINES

Aminoglycosides are currently recommended in patients with cavitary disease, treatment failures, and those who have been treated previously. These drugs have potent antimycobacterial activity but little is known about long-term outcomes with their use in MAC. Kobashi et al conducted a prospective, randomized, controlled study of the clinical efficacy of streptomycin in the treatment of pulmonary MAC. Patients were randomized to received streptomycin versus placebo, administered intramuscularly at 15 mg/kg three times per week for the initial 3 months of therapy in combination with oral clarithromycin, rifampin, and ethambutol. The sputum conversion rate at completion of therapy was significantly better in the streptomycin group; however, there were no significant differences in the sputum relapse rate and clinical improvement, including both clinical symptoms and radiological findings.[20]

The British Thoracic Society[21] recently reported the results of a large randomized, controlled trial for the treatment of MAC pulmonary disease. They compared clarithromycin versus ciprofloxacin as the third drug added to ethambutol and rifampin for treatment of pulmonary MAC, *M. malmoense*, and *M. xenopi*. Doses used in the trial were those recommended by the ATS for daily treatment of cavitary disease. Ciprofloxacin was dosed as 750 mg by mouth twice daily. Patients' clinical and bacteriologic progress was documented annually during the 2 years of treatment and for 3 years thereafter. If at 1 year a patient was not improving, the regimen was

Table 4 Treatment Regimens for *Mycobacterium avium* Complex Lung Disease

Nodular/Bronchiectatic Disease	Cavitary Disease	Advanced/Previously Treated Disease
Clarithromycin 1000 mg tiw or azithromycin 500–600 mg tiw	Clarithromycin 500*–1000 mg daily or azithromycin 250–300 mg daily	Clarithromycin 500*–1000 mg daily or azithromycin 250–300 mg daily
Ethambutol 25 mg/kg tiw	Ethambutol 15 mg/kg daily	Ethambutol 15 mg/kg daily
Rifampin 600 mg tiw	Rifampin 450*–600 mg daily	Rifampin 450*–600 mg daily or rifabutin 150*–300 mg daily
Aminoglycoside—none	Streptomycin 15 mg/kg IV/IM† or amikacin 15 mg/kg IV/IM	Streptomycin 15 mg/kg IV/IM† or amikacin 15 mg/kg IV/IM

*Lower dose for weight < 50 kg.
†For older patients with nodular/bronchiectatic disease or for patients who require a prolonged course (i.e., >6 months), some experts recommend 8 to 10 mg/kg/day two to three times per week.
Adapted from Griffith et al.[6]

supplemented by the addition of the one drug that had not been allocated originally.

After the completion of therapy clinical and bacteriology status of patients were assessed annually. The primary end points were failure of treatment or relapse. One hundred and seventy patients with pulmonary MAC were included in the study. There was no significant difference in the number of patients who completed therapy and were "alive and well" at 5 years (24% in the clarithromycin group vs 23% in the ciprofloxacin group). Failure and relapse rates for the clarithromycin versus ciprofloxacin groups were 4.8% versus 14.9% and 8.4% versus 8%, respectively. These outcomes appear dismal compared with the studies reviewed by Field et al.[8] Two explanations include the high percentage of cavitary disease among this population (69% in the clarithromycin group versus 63% in the ciprofloxacin group) and the high all-cause mortality. Forty-six percent of patients in the clarithromycin arm and 23% in the ciprofloxacin arm died of causes other than that due to mycobacterial disease.

HRCT findings may be able to predict response to therapy. Kuroishi et al found that atelectasis, cavities, and pleural thickening in HRCT findings were significantly more frequent among patients unable to convert their sputum cultures to negative versus those in the converted group. In addition, the extent of pulmonary involvement of bronchiectasis, atelectasis, cavities, and pleural thickening was significantly greater in the nonconverted group.[22]

DISSEMINATED DISEASE

Disseminated disease occurs almost exclusively in immunocompromised hosts. With the advent of the AIDS epidemic, disseminated MAC was one of the most common opportunistic infections recognized. *M. avium* is the etiologic agent responsible for greater than 95% of cases of disseminated disease in HIV-infected persons. Most cases occur in patients with a CD4 lymphocyte count less than 50 cell/μL.[23] A study by Chin et al found that isolation of MAC from the respiratory or gastrointestinal tract had an association with development of bacteremia (relative hazards for respiratory and gastrointestinal tract, 2.3 and 6.0; 95% confidence intervals, 1.1 to 4.6 and 2.5 to 14.6, respectively).[24] Epidemiological associations have been made such as outbreaks linked to water sources via genotyping.[25] Clinical symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain. The most commonly identified laboratory abnormalities include anemia and elevated alkaline phosphatase.[26] Diagnosis of disseminated MAC is made with a combination of clinical signs and symptoms coupled with the isolation of MAC from blood, bone marrow, or other normally sterile tissue or body fluids.[27]

Treatment of Disseminated MAC

Antimicrobial treatment of disseminated MAC includes at least two agents, the first of which is a macrolide, either clarithromycin or azithromycin. Ethambutol is the recommended second agent. Monotherapy is never advised in the treatment of MAC because of the concern for developing resistance. Adding a third agent such as rifabutin is controversial. Before effective antiretroviral therapy was available, one randomized, controlled trial noted improved survival with the addition of rifabutin to a treatment regimen, and two randomized, controlled trials noted a reduced emergence of macrolide resistance.[28,29]

Successful treatment of disseminated MAC relies on recovery of the immune system. Highly active antiretroviral therapy is imperative in the setting of disseminated MAC and AIDS. Antiretrovial therapy should be initiated simultaneously or 1 to 2 weeks after beginning antibiotics.[27] It is important to follow patients closely for evidence of an immune reconstitution syndrome that can develop after the initiation of antiretroviral therapy.[30–32] Antimycobacterial therapy can be discontinued once a patient has met all of the following criteria: completed ≥ 12 months of therapy, remains asymptomatic, and sustains (>6 months) a CD4 count >100 cells/μL.[27]

SKIN AND SOFT TISSUE AND BONE INFECTION

MAC infection can present as cutaneous lesions, abscesses, lymphadenitis, arthritis, tenosynovitis, or osteomyelitis. Risk factors include traumatic injury to the skin, recent surgery, corticosteroid injection, or immune reconsitution as in the setting of AIDS. Soft tissue abscesses and lymphadenitis due to MAC after the initiation of highly active antiretroviral therapy are well described in the literature.[30–32] Reports from soft tissue infections in immunocompromised populations such as patients receiving antirheumatoid agents are emerging as well.[33] Septic arthritis is an unusual clinical manifestation that is frequently overlooked initially.[34] MAC can also cause a granulomatous tenosynovitis, which may be preceded by a surgical procedure, trauma, or corticosteroid injection.[35] (Fig. 3)

In children, cervical lymphadenitis represents the predominant manifestation of NTM infection.[36] Diagnosis is made by aspiration of a lymph node or tissue culture, with the latter having a greater sensitivity. Excisional surgery without chemotherapy is the recommended treatment for children with MAC lymphadenitis.[6] In cases of localized infection with immune reconstitution, surgery is not routinely recommended. In all other presentations a combination of surgery and antimicrobials is curative in most patients.[37] The recommended drug regimen is the same as for MAC pulmonary

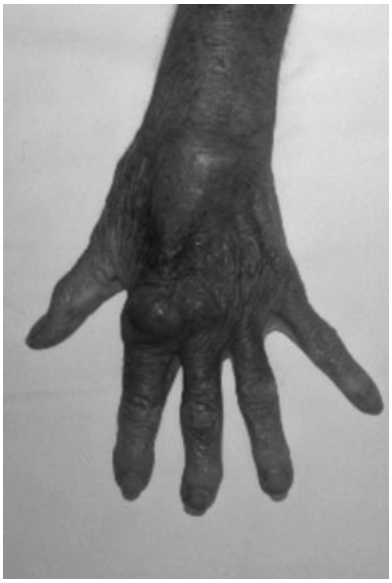

Figure 3 Left hand tenosynovitis due to *Mycobacterium avium* complex infection in a 70-year-old woman.

disease, and the optimal duration is unknown, but 6 to 12 months of treatment is usually recommended.[6]

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP) occurs with exposure to aerosols containing mycobacteria, most notably in hot tub users ("hot tub lung"). A recent report from Rochester, Minnesota, studied consecutive patients with HP presenting to their institution between 1997 and 2002.[38] The etiology was identified in 75% of cases (64/85). Twenty-one percent were due to MAC in the water of hot tubs. The symptoms of HP secondary to MAC are dyspnea, cough, and fever.[39] The computed tomographic findings are most commonly diffuse centrilobular nodularity, ground-glass attenuation, and evidence of air trapping on expiratory images.[40] In one review of 21 cases of hot tub lung, all patients had MAC isolated from their hot tub, respiratory secretions, and/or lung tissue.[41] Eighteen patients had a lung biopsy performed that demonstrated bronchiolocentric granulomatous inflammation. In this study, antimycobacterial therapy was infrequently required in the management. Only 15% of patients received antibiotics and all patients recovered with avoidance of the exposure or a combination of avoidance and corticosteroids (62%). Finally, it should be emphasized that this HP picture secondary to MAC can be acquired from other aerosols as well. Exposure to metal-working fluids and showering are other potential activities that can lead to HP.[39,42,43]

CONCLUSION

MAC disease syndromes are well described and recognized in normal and immunocompromised hosts. Unlike with tuberculosis, isolation of a single positive sputum culture does not necessarily represent disease so diagnostic criteria have been developed to aid the clinician in deciding whether treatment is indicated. Unfortunately, well-designed and appropriately powered studies for the treatment of immunocompetent hosts are still lacking. Until the results of such studies are available, the recommended treatment regimen for pulmonary disease is a three-drug macrolide-based regimen. Extrapulmonary disease is increasing in frequency and is more likely to require surgical intervention than pulmonary disease. Sadly, prevention of MAC infections remains elusive given our poor understanding of host factors, organism characteristics, and environmental exposure.

REFERENCES

1. Turenne CY, Wallace RJr, Behr MA. *Mycobacterium avium* in the postgenomic era. Clin Microbiol Rev 2007;20:205–229
2. Falkinham JO III. Nontuberculous mycobacteria in the environment. Clin Chest Med 2002;23:529–551
3. Marras TK, Daley CL. Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 2002;23:553–567
4. Khan K, Wang J, Marras TK. Nontuberculous mycobacterial sensitization in the United States: national trends over three decades. Am J Respir Crit Care Med 2007;176:306–313
5. Marras TK, Chedore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997 2003. Thorax 2007;62:661–666
6. 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
7. Pasteur MC, Helliwell SM, Houghton SJ, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000;162(4 Pt 1): 1277–1284
8. Field SK, Fisher D, Cowie RL. *Mycobacterium avium* complex pulmonary disease in patients without HIV infection. Chest 2004;126:566–581
9. Dautzenberg B, Piperno D, Diot P, Truffot-Pernot C, Chauvin JP. Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Clarithromycin Study Group of France. Chest 1995;107:1035–1040
10. Wallace RJ Jr, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for *Mycobacterium avium–intracellulare* complex lung disease. Am J Respir Crit Care Med 1994;149:1335–1341
11. Griffith DE, Brown BA, Girard WM, Murphy DT, Wallace RJ Jr. Azithromycin activity against *Mycobacterium avium* complex lung disease in patients who were not infected with human immunodeficiency virus. Clin Infect Dis 1996;23:983–989
12. Kobashi Y, Yoshida K, Miyashita N, Niki Y, Oka M. Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates. J Infect Chemother 2006;12:195–202
13. Kobashi Y, Matsushima T. The microbiological and clinical effects of combined therapy according to guidelines on the treatment of pulmonary *Mycobacterium avium* complex disease

in Japan—including a follow-up study. Respiration 2007;74: 394–400
14. Kuwabara K, Tsuchiya T. Clinical features and treatment history of clarithromycin resistance in *M. avium–intracellulare* complex pulmonary disease patients [in Japanese]. Nihon Kokyuki Gakkai Zasshi 2007;45(8):587–592
15. Griffith DE, Brown-Elliott BA, Langsjoen B, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 2006;174:928–934
16. Kohno Y, Ohno H, Miyazaki Y, et al. In vitro and in vivo activities of novel fluoroquinolones alone and in combination with clarithromycin against clinically isolated *Mycobacterium avium* complex strains in Japan. Antimicrob Agents Chemother 2007;51:4071–4076
16a. Kasperbauer S, Wilson SE, Graham JJ, Heifets L, Daley C. Fluoroquinolone susceptibility in non-tuberculous mycobacteria. Presented at: The American Thoracic Society International Conference; May 23, 2007; San Francisco, CA: Abstract p. 971
17. Griffith DE, Brown BA, Girard WM, Griffith BE, Couch LA, Wallace RJ Jr. Azithromycin-containing regimens for treatment of *Mycobacterium avium* complex lung disease. Clin Infect Dis 2001;32:1547–1553
18. Griffith DE, Brown BA, Cegielski P, Murphy DT, Wallace RJ Jr. Early results (at 6 months) with intermittent clarithromycin-including regimens for lung disease due to *Mycobacterium avium* complex. Clin Infect Dis 2000;30:288–292
19. Lam PK, Griffith DE, Aksamit TR, et al. Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 2006;173: 1283–1289
20. Kobashi Y, Matsushima T, Oka M. A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary *Mycobacterium avium* complex disease. Respir Med 2007;101:130–138
21. Jenkins PA, Campbell IA, Banks J, Gelder CM, Prescott RJ, Smith AP. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of Mycobacterium vaccae immunotherapy. Thorax 2008;63:627–634
22. Kuroishi S, Nakamura Y, Hayakawa H, et al. Mycobacterium avium complex disease: prognostic implication of high-resolution computed tomography findings. Eur Respir J 2008;32:147–152
23. Horsburgh CR Jr. *Mycobacterium avium* complex infection in the acquired immunodeficiency syndrome. N Engl J Med 1991;324:1332–1338
24. Chin DP, Hopewell PC, Yajko DM, et al. *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *M. avium* complex bacteremia in patients with human immunodeficiency virus infection. J Infect Dis 1994; 169:289–295
25. von Reyn CF, Maslow JN, Barber TW, Falkinham JO III, Arbeit RD. Persistent colonisation of potable water as a source of *Mycobacterium avium* infection in AIDS. Lancet 1994;343:1137–1141
26. Benson CA. Disease due to the *Mycobacterium avium* complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis 1994;18(Suppl 3):S218–S222
27. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/ Infectious Diseases Society of America. MMWR Recomm Rep 2004;53(RR-15):1–112
28. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. Clin Infect Dis 2003;37:1234–1243
29. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. Clin Infect Dis 1999;28:1080–1085
30. Corti M, Villafane MF, Ambroggi M, Sawicki M, Gancedo E. Soft tissue abscess and lymphadenitis due to *Mycobacterium avium* complex as an expression of immune reconstitution inflammatory syndrome after a second scheme of highly active antiretroviral therapy. Rev Inst Med Trop Sao Paulo 2007;49: 267–270
31. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005;41:1483–1497
32. Shelburne SA III, Hamill RJ. The immune reconstitution inflammatory syndrome. AIDS Rev 2003;5:67–79
33. Salvana EM, Cooper GS, Salata RA. *Mycobacterium* other than tuberculosis (MOTT) infection: an emerging disease in infliximab-treated patients. J Infect 2007;55:484–487
34. Olsen RJ, Cernoch PL, Land GA. Mycobacterial synovitis caused by slow-growing nonchromogenic species: eighteen cases and a review of the literature. Arch Pathol Lab Med 2006;130:783–791
35. Hellinger WC, Smilack JD, Greider JL Jr, et al. Localized soft-tissue infections with *Mycobacterium avium/Mycobacterium intracellulare* complex in immunocompetent patients: granulomatous tenosynovitis of the hand or wrist. Clin Infect Dis 1995;21:65–69
36. Maltezou HC, Spyridis P, Kafetzis DA. Nontuberculous mycobacterial lymphadenitis in children. Pediatr Infect Dis J 1999;18:968–970
37. Liao CH, Lai CC, Ding LW, et al. Skin and soft tissue infection caused by non-tuberculous mycobacteria. Int J Tuberc Lung Dis 2007;11:96–102
38. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. Mayo Clin Proc 2007;82:812–816
39. Marras TK, Wallace RJ Jr, Koth LL, Stulbarg MS, Cowl CT, Daley CL. Hypersensitivity pneumonitis reaction to *Mycobacterium avium* in household water. Chest 2005; 127:664–671
40. Hartman TE, Jensen E, Tazelaar HD, Hanak V, Ryu JH. CT findings of granulomatous pneumonitis secondary to *Mycobacterium avium–intracellulare* inhalation: "hot tub lung". AJR 2007;188:1050–1053
41. Hanak V, Kalra S, Aksamit TR, Hartman TE, Tazelaar HD, Ryu JH. Hot tub lung: presenting features and clinical course of 21 patients. Respir Med 2006;100:610–615
42. Centers for Diseases Control and Prevention. Respiratory illness in workers exposed to metalworking fluid contaminated with nontuberculous mycobacteria—Ohio, 2001. JAMA 2002; 287:3073–3074
43. Centers for Disease Control and Prevention (CDC). Respiratory illness in workers exposed to metalworking fluid contaminated with nontuberculous mycobacteria—Ohio, 2001. MMWR Morb Mortal Wkly Rep 2002;51:349–352