Pulmonary Disease

Pulmonary Mycobacterium avium-intracellulare Complex Infection in the Immunocompetent Host

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INTRODUCTION

Nontuberculous mycobacteria (NTM) were first described in the late 19th century following Koch’s discovery of the tubercle bacillus in 1882. It was not until the 1950s, however, that NTM were recognized as important pathogens, when they were shown to cause disease in patients with established, severe chronic lung disease, such as bronchiectasis secondary to healed tuberculosis. Early on in the AIDS epidemic, Mycobacterium avium was shown to cause disseminated infections in severely immunocompromised hosts. Subsequently, the Mycobacterium avium-intracellulare complex (MAC) was implicated as a cause of lung disease in immunocompetent patients with no preexisting lung disease.1 It is now recognized that the MAC organisms are not just colonizers but rather represent pathogens that must be treated in most patients. Despite increased awareness of MAC as a pathogen as well as recent advances in diagnostic techniques and treatment, the management of patients with MAC continues to be challenging for several reasons, including the long duration of treatment, poor sputum conversion rates, antibiotic resistance, and noncompliance with therapy. This manual reviews the diagnosis and treatment of MAC pulmonary disease in immunocompetent patients.

When first isolated, M. avium and M. intracellulare were classified together as M. avium-intracellulare complex (MAC) because of difficulty in distinguishing between the 2 organisms. For most purposes, infections with these organisms are considered together, although there are subtle differences between them. In this manual, we use the term MAC to refer to the complex, which also includes Mycobacterium X, where X represents undesignated species of mycobacteria.

EPIDEMIOLOGY

NTM are ubiquitous in the environment. They have been isolated from soil and water,2,3 which appear to be the reservoir for most infections, as well as from poultry, swine, birds, and reptiles. It was initially postulated that birds may act as a reservoir for infection, but studies suggest that animal-to-human transmission is not important. There is no evidence demonstrating that person-to-person transmission occurs.4 Pulmonary disease from MAC infection in immunocompetent hosts usually affects hosts with preexisting lung disease. The pathogenic nature of MAC organisms in immunocompetent patients without preexisting lung disease was demonstrated by Prince and colleagues in 1989.1

In a landmark study, Palmer performed skin testing with 5 tuberculin units (TU) on more than 22,000 nursing students after taking a complete history of geographic residence.5 The presence of an induration larger than 5 mm was considered a positive result, and patients with negative results were retested with 250 TU. Analysis of the subjects with negative results on 5 TU testing showed a median reaction of 7 mm to the 250 TU dose in those who lived exclusively in the southeastern United States, with 65% having a reaction of at least 5 mm. There was a median reaction of 0 mm in subjects from other parts of the United States. The degree of tuberculosis exposure obtained by history was not related to the reaction to the 250 TU dose. The author proposed that these patients were infected with antigenically similar organisms.5 Subsequently, Gruft et al obtained water and air samples along the East Coast and found that the regional distribution of the highest number of MAC strains coincided with the areas of skin-test reactors as determined by earlier studies.6 The preponderance of MAC in the southeast probably is related to the warmer temperature in this region given that the organisms grow best above 17.8°C, but other unknown factors may play a role. Interestingly, disseminated MAC in AIDS, unlike pulmonary disease, does not seem to have a geographic preference in the United States.7

Because MAC infection is not a reportable disease in the United States, obtaining accurate information about
its incidence and prevalence has been challenging. However, a number of epidemiologic studies point toward an increasing incidence and prevalence of the disease worldwide.\(^8,9\) The prevalence of NTM infection is estimated to be 1.8 cases per 100,000 persons in the United States, with MAC infection accounting for more than 60% of these cases (1.1 cases per 100,000 persons).\(^9\) MAC now may account for more cases of mycobacterial infection than tuberculosis. This increase may reflect greater awareness of the clinical manifestations of the disease as well as better microbiologic techniques for isolating the organisms.

### PATHOGENESIS

In patients with HIV infection, disseminated MAC infection is believed to be caused by organisms that translocate through the intestinal mucosa. MAC organisms can resist the acidic environment in the stomach and may develop resistance to extremely acidic conditions (pH < 3).\(^10\) This property allows the organisms to bypass the highly acidic gastric mucosa and enter the terminal ileum, where they bind to the enterocytes.\(^11\) Once inside the enterocyte, they appear to inhibit the uptake of local chemokines. After leaving the enterocytes, the organisms locate to the mesenteric lymph nodes where they can survive for many years prior to dissemination.

MAC pulmonary infection seems to be acquired by inhalation.\(^22\) However, the pathogenesis of pulmonary disease caused by MAC infection is not well understood. Martinez et al demonstrated that MAC organisms are able to form biofilms by producing glycopeptolipids, which the authors hypothesized could provide a means of surface motility; isolates that did not produce glycopeptolipids were unable to translocate on surfaces.\(^13\) This property of MAC organisms may play a role in colonization of the upper airway, but its significance in clinical infection remains to be determined. Once the organisms reach the alveolar space, they invade type 2 alveolar epithelial cells;\(^14\) however, MAC organisms do not induce epithelial cells to secrete chemokines (monocyte chemotactic protein-1 and interleukin-8).\(^15\) These local factors may allow the organisms to colonize the small airways.

### HOST SUSCEPTIBILITY FACTORS

Traditionally MAC was dismissed as a “colonizer” and was thought to be a rare cause of disease in immunocompetent patients with normal lungs. However, the landmark Prince et al paper demonstrated that MAC can cause disease in persons without preexisting lung disease or damage.\(^1\) Using computed tomography (CT) scanning, researchers have identified nodules and bronchiectasis in patients who were previously thought to be only colonized with MAC. Thus, it is likely that in patients with repeated positive cultures for MAC, the organism is in fact a pathogen. Accordingly, researchers have studied specific subsets of patients who develop MAC infection in order to identify factors that may render these patients susceptible to clinical disease.

#### Genotypic Factors

Case reports documenting familial clusters of MAC infections in non–HIV patients have prompted a search for a possible genetic basis for development of disease.\(^16,17\) Goto et al showed that the natural resistance-associated macrophage protein (NRAMP1) gene is the single dominant gene that controls resistance to MAC in mice.\(^18\) Subsequently, Tanaka et al investigated whether defects in the NRAMP1 gene were responsible for the increased susceptibility in 2 persons with familial MAC; however, they were unable to find the genetic variations identified in murine models.\(^16\) Dorman and Holland demonstrated that genetic defects in the interferon (IFN)-\(\gamma\) receptors could play a role in increasing susceptibility to MAC infections.\(^19\) Other studies have shown increased susceptibility to MAC infections in patients with mutations in the interleukin-12R\(\beta1\) receptor gene.\(^20\) Holland et al reported that a family with disseminated MAC infection showed some improvement following treatment with IFN-\(\gamma\), suggesting that IFN has an important role in the development of MAC infections.\(^21\)

#### Phenotypic Factors

MAC pulmonary disease has been recognized to occur in immunocompetent patients with normal lungs and specific phenotypes (ie, thin women with thoracic spine abnormalities and mitral valve prolapse). Iseman and colleagues observed that pectus excavatum and thoracic scoliosis occurred more frequently in patients with pulmonary disease due to MAC than in patients with tuberculosis or in the general population.\(^22\) They proposed that patients without predisposing conditions who develop MAC may possess phenotypic factors arising from genetic defects that affect body morphology and that these factors can serve as markers of increased risk for MAC infection.

#### Female Sex Hormones

Tsuyuguchi et al found that ovariectomized mice who were experimentally infected with MAC had a...
decreased bacterial load and enhanced macrophage response following administration of exogenous estrogen compared with control mice. This finding suggests that a lack of endogenous estrogen may play a role in the development of MAC infections in postmenopausal women.

**Cellular Immunity**

In patients with HIV infection, MAC infections are usually seen at CD4+ T cell counts below 50/mm³, suggesting that cellular immunity, particularly the CD4+ T cell and the T-cell-receptor-γδ-bearing cell, plays an important role in host immune response to these organisms. Tsukaguchi et al suggested that the decline in growth inhibition of MAC in non-HIV patients may result from T-cell-specific dysfunction wherein the T cell is only partially impaired. Such selective dysfunction may explain why immunocompetent patients do not show disseminated disease, unlike HIV patients, who have an absolute decrease in the number of T cells.

**CLINICAL FEATURES**

The clinical presentations of pulmonary MAC infection in immunocompetent hosts can be divided into 3 groups: preexisting lung disease, no preexisting disease, and rare/atypical presentations. Chronic pulmonary disease resembling tuberculosis is the most common presentation of pulmonary MAC infection in patients with preexisting chronic obstructive pulmonary disease (COPD). This presentation occurs primarily in white men aged 40 to 60 years who smoke and may have a history of alcoholism. The disease seen in these patients is apical fibrocavitary disease. Lung diseases other than COPD associated with the development of MAC pulmonary disease include previous tuberculosis and other granulomatous disease, radiation fibrosis, silicosis, cystic fibrosis, chronic aspiration and esophageal disease, alcoholism, bronchiectasis, bronchogenic carcinoma, allergic bronchopulmonary aspergillosis, and coal workers’ pneumoconiosis. Occupations known to be associated with an increased risk for atypical mycobacterial infections include sandblasting (silicosis), coal mining, and arc welding.

The signs and symptoms of pulmonary MAC are variable and nonspecific, with cough being the most common complaint. Constitutional symptoms of anorexia, weight loss, night sweats, and failure to thrive become more prominent as the disease progresses but are seen in less than 20% of patients. Hemoptysis may occur secondary to bronchiectasis or endobronchial disease or as a manifestation of the preexisting lung disease.

A second presentation involving patients with pulmonary MAC infections who have no preexisting disease has been identified more recently. In the Prince et al study, 81% of the patients were women, and productive cough was the primary symptom, whereas hemoptysis, dyspnea on exertion, and constitutional symptoms were uncommon. A subsequent study found cough to be the most common presenting symptom, with constitutional symptoms becoming more prominent as the disease progressed. The typical presentation in patients without preexisting lung disease includes chronic nonproductive cough, fever, fatigue, unexplained weight loss, and other nonspecific symptoms. Reich et al reported a series of patients with MAC pulmonary disease with the following features: (1) involvement of the right middle lobe and the lingula; (2) absence of preexisting pulmonary disease; and (3) exclusivity of these features to female patients. Noting that the lingula and the right middle lobe have long narrow bronchi and require greater tussive effort for satisfactory bronchopulmonary clearing, the authors hypothesized that voluntary suppression of cough in these patients led to the development of postobstructive pneumonitis and focal bronchiectasis in these lobes. They called this constellation of findings Lady Windermere syndrome, after the Victorian era play, to convey the fastidious behavior in older female patients who are more likely to regard expectoration as socially unacceptable behavior. Several other studies have reported this presentation in middle-aged women who were predominantly white or Asian, did not smoke, and had a thin body habitus with pectus excavatum and other thoracic abnormalities, suggesting the role of a specific phenotype in developing this disease, as described earlier.

Rare and atypical presentations include pleuritis and effusion and solitary pulmonary nodules. Lymphadenopathy is uncommon, occurring in approximately 5% of cases.

**RADIOLOGIC FEATURES**

The radiologic features of MAC pulmonary disease historically were considered to be similar to *M. tuberculosis* infection. Early reviews of the radiographic manifestations of MAC reported a high incidence of cavitary lesions. Christensen et al noted that in 114 patients with at least 2 positive sputum cultures for MAC and no history of tuberculosis, 7 had normal chest radiographs and 7 had reticulonodular-appearing disease. Of the remaining 100 patients, 92% had infiltrates in the
upper lobes, 88% had cavitary disease, and 70% had scarring and volume loss. Subsequent studies have noted a much lower incidence of cavitary lesions, ranging from 38% to 43% (Table 1). Some of the changes in radiologic findings may be due to increased recognition of MAC infection in patients without pre-existing lung disease. These patients typically are non-smokers and most commonly present with multiple pulmonary nodules (Figure 1). Men more frequently have cavitary lesions (Figure 2). In this subset of patients, the presentation is usually small centrilobular nodules and cylindrical bronchiectasis involving the right middle lobe and lingula.

CT scanning is extremely helpful because it can demonstrate the number and distribution of nodules and define the “tree in bud” pattern suggestive of MAC infection (Figure 3). The differential diagnosis of this pattern includes tuberculosis, viral pneumonias, diffuse panbronchiolitis, allergic bronchopulmonary aspergillosis, and aspiration. Tuberculosis and MAC pulmonary disease have similar features on CT scanning, with bronchiectasis being more common in MAC disease and interlobular septal thickening more common in tuberculosis. Bronchiectasis may be missed on routine radiographs and is better evaluated on high-resolution CT scans. Wittram and Weisbrod attempted to correlate chest radiograph and CT scan findings in MAC infection and found that CT often identified abnormal lobes thought to be normal based on chest radiograph (Table 2).

Table 1. Radiologic Features of MAC Pulmonary Disease

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Feature</th>
<th>Patients with Feature, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen et al (114)</td>
<td>Upper lobe infiltrates, apical/posterior</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Cavitary lesions</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Atelectasis/scarring</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Adenopathy</td>
<td>&lt; 5</td>
</tr>
<tr>
<td></td>
<td>Endobronchial spread</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td>5</td>
</tr>
<tr>
<td>Woodring et al (40)</td>
<td>Linear shadows and nodules with/without calcification</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Consolidation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Upper lobe involvement, apical/posterior</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Mass-like densities</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Cavitary lesions</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Pleural effusions</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Apical pleural thickening</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
<td>5</td>
</tr>
<tr>
<td>Albelda et al (35)</td>
<td>Upper lobe disease</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Cavitary lesions</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Solitary nodule</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Adenopathy</td>
<td>0</td>
</tr>
</tbody>
</table>

MAC = Mycobacterium avium-intracellulare complex.

Figure 1. Chest radiograph demonstrating multiple pulmonary nodules.

Figure 2. Computed tomography scan demonstrating cavitary lesions from Mycobacterium avium-intracellulare complex infection. This patient eventually underwent surgical resection.
Air trapping seen on CT scan has been described in patients with MAC lung disease. In a study that compared pulmonary function tests and high-resolution CT scans in patients with pulmonary MAC and normal subjects, Kubo et al found that forced expiratory flow at 25% and 75% of forced vital capacity was significantly lower in patients with MAC, suggesting small airway disease. Patients with MAC also had increased residual volume and residual volume/total lung capacity. Air trapping on high-resolution CT manifests as areas of hypolucency, often in the upper lung fields.

Uncommon presentations of pulmonary MAC, such as focal nodules or masses, are usually asymptomatic and the diagnosis is made at resection. In a series looking at 20 patients with resected solitary nodules and positive acid-fast bacilli over 10 years, 60% of the patients had MAC infection. Most of these patients had been treated for presumed tuberculosis without any subsequent dissemination. The size of the nodules ranged from 1.1 cm to 1.5 cm, and there was no specific predilection for any lobe. Pleural effusion is a relatively infrequent finding, reported in 5% to 15% of patients with pulmonary MAC.

**DIAGNOSIS**

The diagnosis of pulmonary MAC infection is based on a combination of clinical, radiologic, and microbiologic criteria (Table 3). The 1997 American Thoracic Society (ATS) guidelines summarize these criteria based on the patients’ immune status (alcoholism, bronchiectasis, cyanotic heart disease, cystic fibrosis, prior mycobacterial disease, pulmonary fibrosis, smoking/COPD, HIV infection, general immune suppression, none). A typical presentation, such as a patient with history of COPD, chronic cough with features of cavitary disease on chest radiograph, and several positive cultures from sputum samples or bronchoscopy over a 12-month period, makes the diagnosis relatively easy. In patients without typical features, a combination of the clinical, radiographic, and microbiologic criteria as well as knowledge of their immune status is needed to make a diagnosis. Lung biopsy is not essential but may be needed in patients with nondiagnostic cultures and radiologic studies. Presence of granulomatous inflammation on the tissue biopsy is sufficient to establish the diagnosis, and acid-fast bacilli positivity is not required. Cultures using samples gathered by transbronchial biopsy may be negative due to small sample size.

### Table 2. Abnormalities of MAC Pulmonary Disease on Radiograph versus CT Scan

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Radiograph (n = 26)</th>
<th>CT Scan (n = 26)</th>
</tr>
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<tbody>
<tr>
<td>Atelectasis</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Cavities</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Consolidation</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Emphysema*</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Ground-glass opacities</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Linear opacities</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Mediastinal nodes</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Overinflation</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Pleural disease</td>
<td>13</td>
<td>15†</td>
</tr>
</tbody>
</table>

CT = computed tomography; MAC = *Mycobacterium avium*-intracellulare complex.

*b Bullae on radiograph, centrilobular on CT scan.
†Thickening 14, fluid 1.

**TECHNIQUES FOR DETECTION OF MAC**

**Smear Examination**

The examination for acid-fast bacilli is a fundamental part of diagnosing mycobacteria on smear. An organism burden of at least 10,000 acid-fast bacilli is required for the result of this test to be positive. Mycobacteria are termed “acid-fast” because their cell walls bind basic fuchsin dyes and are not decolorized by alcohol. Acid-fast bacilli stain red and non-acid-fast organisms stain blue with the Ziehl-Neelsen stain. False-positive smears...
can result from environmental contamination as well as from cross-contamination from other species. False-negative smears may result from a low organism load or from stains that are either too thin or too thick.

**Culture**

The Middlebrook 7H10 or 7H11 agars are the preferred solid culture media for growing MAC because they provide a higher recovery rate and ease of quantitation. Quantitation of growth on agar plates (ranging from 0 to 4+) is important to estimate clinical significance as well as response to therapy. Liquid media include the radio-labeled BACTEC 12B broth and the non-radio–labeled ESP culture system. The organisms usually produce detectable growth in 2 to 4 weeks on solid media and in 1 to 2 weeks in the BACTEC system. Cultures are generally incubated at 35°C to 37°C for 6 weeks. The BACTEC TB 460 system can differentiate between *M. tuberculosis* and NTM by using a substance called NAP (p-nitro-α-acetylamino-β-hydroxypropiophenone), which is a selective inhibitor of *M. tuberculosis* complex species and inhibits growth of *M. tuberculosis* (but not NTM) at a concentration of 5 µg/mL.

The time needed to identify MAC organisms has been significantly reduced by the use of nucleic acid probes that hybridize with the organisms. These probes can be used with either solid or broth culture media. In this method, acridinium ester-labeled DNA probes form RNA-DNA hybrids with the target nucleic acids. The acridinium esters are then removed from the unbound probes by another agent, but the ester on the hybrids is protected. The chemiluminescence from the acridinium ester on the DNA-RNA hybrids is then detected and used to identify the organism.

**Role of Skin Testing**

Historically, it has been known that patients with MAC display weakly positive reactions to purified protein derivative (PPD) or reactions to much higher doses of PPD, a phenomenon that was used in several early epidemiologic studies of NTM. von Reyn et al studied the use of purified proteins derived from MAC to distinguish between patients infected with *M. tuberculosis* and MAC. A skin test was defined as *M. avium*-dominant or PPD (*M. tuberculosis*)-dominant if there was a reaction size of at least 5 mm to the given species and the reaction to the given species was at least 3 mm greater than the reaction to the heterologous species. They concluded that the specificity of a dominant skin test for MAC was 100%. In a subsequent study using *M. avium* sensitin (MAS), the same authors evaluated the role of dual skin testing and concluded that pa-

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**Table 3. Diagnostic Criteria for MAC Pulmonary Disease**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Radiologic criteria</th>
<th>Bacteriologic criteria</th>
</tr>
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<tbody>
<tr>
<td>a. Compatible signs/symptoms (cough, fatigue most common; fever, weight loss, hemoptysis, dyspnea may be present, particularly in advanced disease) with documented deterioration in clinical status if an underlying condition is present</td>
<td>a. Any of the following chest radiograph abnormalities (if baseline films are more than 1 year old, evidence of progression should be present): Infiltrates with or without nodules (persistent ≥ 2 months or progressive) Cavitation Nodules alone (multiple)</td>
<td>a. At least 3 available sputum/bronchial wash samples within 1 year 3 positive cultures with negative AFB smears OR 2 positive cultures and 1 positive AFB smear OR</td>
</tr>
<tr>
<td>b. Reasonable exclusion of other disease (eg, tuberculosis, cancer, histoplasmosis) to explain condition, or adequate treatment of other condition with increasing signs and symptoms</td>
<td>b. Any of the following high-resolution CT scan abnormalities: Multiple small nodules Multifocal bronchiectasis with or without small lung nodules</td>
<td>b. Single available bronchial wash and inability to obtain sputum samples Positive culture with 2+, 3+, or 4+ growth OR Positive culture with a 2+, 3+, 4+ AFB smear OR</td>
</tr>
<tr>
<td>c. Tissue biopsy</td>
<td>c. Tissue biopsy</td>
<td>c. Tissue biopsy</td>
</tr>
<tr>
<td>Any growth on bronchopulmonary tissue sample</td>
<td>Any growth on bronchopulmonary tissue sample</td>
<td>Any growth on bronchopulmonary tissue sample</td>
</tr>
<tr>
<td>Granuloma and/or AFB on lung biopsy with 1 or more positive culture from sputum/bronchial wash</td>
<td>Granuloma and/or AFB on lung biopsy with 1 or more positive culture from sputum/bronchial wash</td>
<td>Granuloma and/or AFB on lung biopsy with 1 or more positive culture from sputum/bronchial wash</td>
</tr>
<tr>
<td>Any growth from usually sterile extrapulmonary site</td>
<td>Any growth from usually sterile extrapulmonary site</td>
<td>Any growth from usually sterile extrapulmonary site</td>
</tr>
</tbody>
</table>

AFB = acid-fast bacilli; CT = computed tomography; MAC = *Mycobacterium avium*-intracellulare complex.

Adapted with permission from Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association. Am J Respir Crit Care Med 1997;156(2 Pt 2):S1–25. 

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tients with mycobacterial disease who have at least a 5 mm reaction to 1 of the 2 proteins and an MAS reaction of 5 mm more than the PPD reaction have a high likelihood of having disease with MAC. Thus, a specific skin test for MAC very similar to the one used for tuberculosis may have a possible role in the diagnosis of pulmonary MAC and in distinguishing it from M. tuberculosis. This test is not commercially available in the United States.

**TREATMENT**

**ANTIMICROBIAL THERAPY**

Regimens

The introduction of newer macrolide drugs represents a major advance in the treatment of MAC pulmonary disease. Currently, the treatment of MAC is based on a multidrug regimen using 3 or 4 drugs that includes one of the newer macrolides. The 1997 ATS guidelines recommend clarithromycin (500 mg daily) or azithromycin (250 mg daily); rifampicin (600 mg daily) or rifabutin (300 mg daily); and ethambutol (25 mg/kg daily for 2 weeks, then 15 mg/kg daily). Streptomycin 2 to 3 times per week should be considered for the first 8 weeks as tolerated, especially in patients with a high load of extracellular organisms (eg, patients with cavitary disease) or extensive disease on radiograph and strongly positive sputum smears. Recent studies have shown that intermittent therapy (ie, 3 times per week) with a clarithromycin-containing regimen may be equally efficacious as a daily regimen for most cases.

As the guideline recommendations indicate, azithromycin can be substituted for clarithromycin, but clarithromycin interacts with rifabutin to increase rifabutin levels while azithromycin does not. Initial studies on macrolides utilized azithromycin, but clarithromycin subsequently was found to be equally if not slightly more efficacious in converting sputum. Wallace et al reported a sputum conversion rate of 92% with a clarithromycin-based, 4-drug regimen, while subsequent studies by Tanaka et al reported a conversion rate of approximately 72%. This discrepancy may have been due to the slightly higher dose of clarithromycin used in the first study and the presence of clarithromycin resistance in the latter study. Also, in the Wallace study there was a difference between the rates of conversion in men and women, with 95% of the men achieving sputum conversion versus 88% of women. Cavitary disease was much more common in men than in women (92% versus 48%).

Wallace et al studied the MAC isolates among patients with chronic lung disease secondary to MAC and found that patients with nodular bronchiectasis (mostly women) had multiple isolates of MAC, whereas patients with cavitary disease (89%) were infected with a single strain of MAC. A subsequent trial by the same authors looking at the clinical implications of these findings showed that reinfection after successful therapy was more common in patients with nodular bronchiectasis. Relapse was rare in patients who had negative cultures for at least 10 consecutive months, and 85% of subsequent infections represented a new infection. In patients who were culture-negative for less than 10 months, subsequent infections represented relapses rather than new infection. None of these relapse isolates was macrolide resistant.

**Monitoring Patient Response**

Acid-fast bacilli smears and cultures of sputum should be obtained monthly during therapy for pulmonary MAC disease to assess response and periodically after completion of therapy to evaluate for possible relapse. The goal of therapy is negative sputum cultures for at least 12 months. Despite advances in therapy, a small percentage of patients will relapse or develop re-infection. Relapses or reinfection may result in part from the presence of multiple isolates, which raises the question of whether DNA strain comparison is needed to make quality decisions in MAC treatment. Such testing, however, is not a part of the current recommendations. Similarly, routine susceptibility testing is not recommended, but it may be useful in patients who remain sputum positive after 6 months of therapy or who relapse.

Most antibiotics used for treatment are associated with significant side effects, and the clinician must monitor for drug toxicities during the course of therapy. A few common adverse effects include abnormal liver function tests with rifampicin and rifabutin, impaired visual acuity and color vision with ethambutol, ototoxicity and nephrotoxicity associated with aminoglycosides, and gastrointestinal side effects with macrolides. Prompt recognition of side effects is crucial as patients may require changes in their dosage or withdrawal of the offending medication.

The treatment of resistant MAC infection poses challenges due to the lack of good long-term data and potential toxicities of alternative agents. Amikacin, ciprofloxacin, and moxifloxacin have been shown to be active against MAC in vitro, but their activity in vivo has not been studied as extensively. In addition, amikacin must be given intravenously, although some
investigators have administered it in aerosolized form. The safety profile of moxifloxacin for long-term treatment has not been well studied. Cycloserine had been used prior to the advent of macrolides but is now reserved only for resistant disease. Clofazimine has been used to treat leprosy and is also active against MAC; however, studies in patients with AIDS suggested it may not be very effective.

SURGERY

Moran et al reviewed the results of surgical management (lung resection) in 37 patients between 1967 and 1981, prior to the introduction of macrolides. Only 2 patients were reported to have persistent MAC infection at 5-year follow-up. More recent studies following the introduction of clarithromycin have found that in the presence of localized disease and macrolide resistance, there is still a role for surgical treatment, although there was a slightly higher morbidity associated with surgery (usually bronchopleural fistulae). The role of surgery in MAC infections, therefore, has diminished with the availability of better chemotherapy. Currently, surgery has a role in treating only patients with localized disease, especially upper lobe cavitary disease; patients who fail to respond to therapy as defined by the presence of positive cultures after 6 continuous months of antibiotics; and patients who are unable to tolerate routine chemotherapy. Surgery also has a role in resection of undiagnosed nodules.

ADJUVANT THERAPY

Bronchial hygiene remains an important element of management of patients with MAC pulmonary disease, especially with the bronchiectatic variety of MAC. Inhaled β-agonists and mucus clearing devices may be helpful. Antibiotics for episodes of gram-negative superinfections also are recommended.

NOVEL THERAPIES

Novel therapies under investigation for the treatment of atypical mycobacterial infection include immunotherapy using IFN, interleukins, phage therapy, and newer antibiotics. Early reports of the role of interferon in the treatment of MAC infection have led to ongoing research into immunotherapy. Holland reported using subcutaneous IFNγ in 25 patients with MAC (unpublished observations). Chatte et al used aerosolized interferon for the treatment of resistant pulmonary MAC, which resulted in a decrease in acid-fast bacilli on smear and on culture. These are case reports, however, and further research is needed before interferon can be recommended as an adjuvant therapy.

Bermudez et al showed that interleukin-2-stimulated natural killer cells could activate macrophages to inhibit the growth of MAC. This property of interleukin-2 could have a potential role in therapy. The use of microorganism-specific phages as a possible treatment for infectious disease was conceived several years ago. Bacteriophages are a group of viruses that can infect bacteria. It has been demonstrated that mycobacteriophage TM4 kills MAC 109 strain in vitro. However, phage therapy for an intracellular infection would require that the phage be internalized into the cell. Broxmeyer et al used M. smegmatis as a vehicle to deliver the phage into the macrophage infected with MAC and noted killing of the MAC within 4 days. A similar effect also was observed for M. tuberculosis.

The use of linezolid along with mefloquine to treat disseminated MAC in a patient with chronic lymphatic leukemia has been reported. N-octanesulfonylacetamide also has been shown to inhibit the growth of MAC. Bermudez et al showed that a regimen with mefloquine, moxifloxacin, and ethambutol could be an alternative to macrolide regimens.

HOT TUB LUNG

Hot tub lung represents a separate clinical entity in the spectrum of MAC-related lung disease. Patients usually present with slowly progressive dyspnea, cough, fevers, and diffuse infiltrates on the chest radiograph. The organism has been isolated in samples obtained from the hot tub water and in some cases tissue specimens. Whether hot tub lung is just an inflammatory (hypersensitivity) reaction, an infectious process alone, or a combination of both remains controversial. Steroids appear to play a role in treatment, however, and all patients seem to improve when the offending antigen is removed, irrespective of the modality of therapy.

PROGNOSIS

With the improved treatment modalities available, the rates of sputum conversion have been around 60% to 80%. A few patients, however, develop long-term consequences of pulmonary MAC infection, including scarring, residual cavities, and bronchiectasis. It is unclear which subsections of patients have a worse prognosis, although rates of sputum conversion are lower in women with the predominantly bronchiectatic form of the disease. In addition, older, thinner patients tend to do worse. As with most infections, patients with
underlying lung disease and comorbid conditions have a poorer prognosis.

Investigators have tried to identify markers to predict which patients with pulmonary MAC will deteriorate despite treatment. Yamakazi et al observed that serum carbohydrate antigen 19-9, a tumor carbohydrate associated antigen and a marker for gastrointestinal malignancies (especially pancreatic), was elevated in patients who deteriorated clinically as compared to patients with a stable course. Yamori et al proposed that patients with disease caused by *M. avium* may be more difficult to cure than *M. intracellularum*. With newer diagnostic tools, it may soon be possible to identify patients with a poor prognosis.

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