Clinical Case of the Month

Mycobacterium avium Complex Pulmonary Disease: Management Options in HIV-Negative Patients

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CME Information

Target Audience

The September/October Clinical Case of the Month is intended for medical students, general practitioners, medicine subspecialists, emergency medicine physicians, radiologists, pathologists, and surgeons.

Educational Objectives

The Clinical Case of the month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these manuscripts. After reading this article, physicians should be better able to identify and to understand the clinical presentation, diagnosis, and the complex treatment options of *Mycobacterium avium* complex pulmonary disease. Estimated time to complete this activity is one (1) hour.

Credit

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure

Drs. Ramirez, Mason, and Ali have nothing to disclose.

Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees. He is also on the *Journal* Editorial Board.

Original Release Date	Expiration Date
9/30/2008	9/30/2009

Objective: We present a case series and review of the literature of the management options in non-HIV-infected patients with *Mycobacterium avium* complex pulmonary disease (MAC-PD) with a focus on treatment failure and drug resistant disease.

Case Series: Five case histories are presented, depicting various clinical scenarios necessitating different approaches to therapy and highlighting the limitations and complications of these options.

Discussion: *Mycobacterium avium* complex (MAC) is well recognized as a significant cause of pulmonary disease in non-HIV infected patients and in those with intact immunity. Isolation of non-tuberculous mycobacteria (NTM) in culture is essential for the diagnosis of NTM lung disease. The typical presentation of MAC lung disease is apical fibrocavitary lung disease in men in their late 40s and early 50s who have a history of cigarette smoking and, frequently, excessive alcohol use. Other presentations of NTM lung disease include nodular bronchiectasis, solitary or multiple pulmonary nodules, and hypersensitivity pneumonitis. When indicated, the standard recommended treatment for most patients is a three- times- weekly regimen of clarithromycin or azithromycin, rifampin, and ethambutol with or without amikacin. Daily therapy is recommended for fibrocavitary disease. Based on published studies, macrolides are the only agents used for treatment of MAC disease for which there is a correlation between in vitro susceptibility and in vivo (clinical) response. Data regarding treatment of macrolide-resistant MAC (MRMAC) and multi-drug resistant MAC (MDRMAC) is sparse. Several drugs have been evaluated in drug-resistant MAC and have potential as effective therapy. Use of multiple drugs to which the isolate is susceptible is preferred to avoid development of future resistance. Surgery in mycobacterial disease is technically difficult, but selected patients with focal disease do benefit from resection of the involved lung.

Conclusions: MAC has protean pulmonary manifestations, especially in those with no recognizable impairments in their immune system. Drug treatment, however, remains difficult with high failure rates and poor long-term sputum conversion. This case series is based on our clinical experience highlighting treatment options and the often unrecognized morbidity and mortality of severe, progressive MAC-PD. It underscores the need for increased awareness of MAC-PD and MDRMAC and the difficulties encountered in their management.

CASE SERIES

Patient 1

A 52-year-old Caucasian woman sought medical attention due to a chronic cough. Physical exam was unremarkable. A computed tomogram (CT) of the chest showed minimal tubular bronchiectasis in the right upper lobe with few small nodules in the right middle lobe (Figure 1). Sputum culture revealed growth of a few colonies of *Mycobacterium avium* complex (MAC). Repeat sputum cultures again revealed a few colonies of MAC. The patient was treated symptomatically and followed clinically by serial sputum tests and radiographic evaluation. No specific therapy for MAC was initiated, and the patient did well.

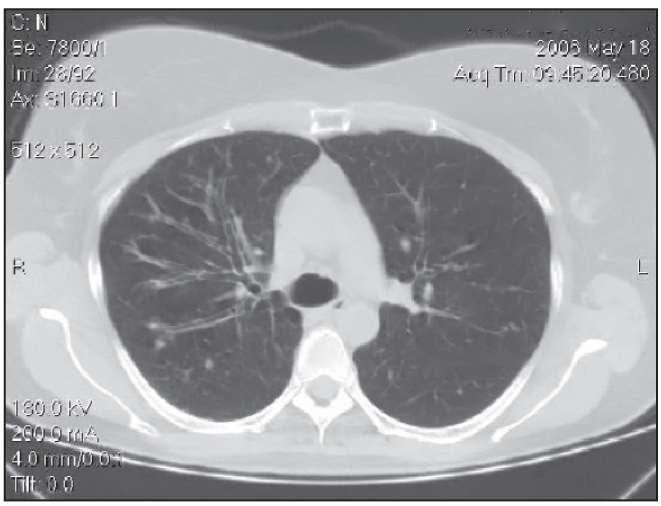

Figure 1. Axial computed tomogram of the chest in patient 1 showing tubular bronchiectasis with nodularity in the right upper lung zone.

Patient 2

A 76-year-old Caucasian woman, a smoker with a past history of tuberculosis, treated completely in the 1960's, presented with cough and minimal shortness of breath. Chest radiography (Figure 2) revealed old tuberculosis scars and a cavity. Pulmonary function tests revealed moderate obstructive airways dysfunction. Sputum tests revealed a moderate growth of *Mycobacterium avium* complex on repeated examinations. The patient was placed on daily treatment with clarithromycin and ethambutol with bronchodilators. She remained stable on this regimen without any acute exacerbations. Serial sputum cultures intermittently revealed a light growth of *Mycobacterium avium* complex.

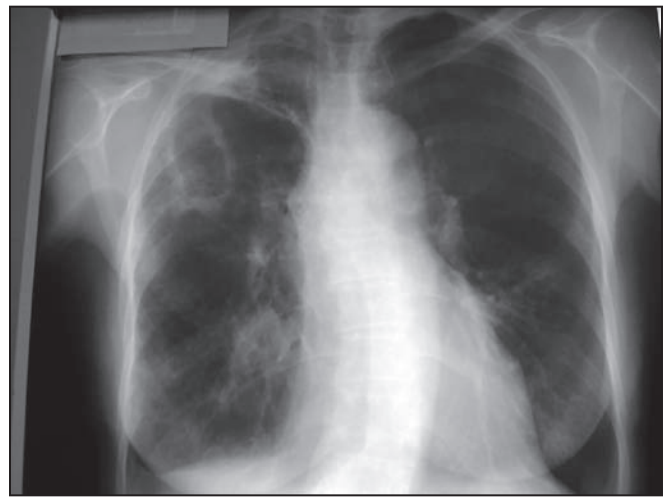

Figure 2. A postero-anterior chest radiograph in patient 2 showing an old tuberculous scar and a large cavity in the right upper lung zone.

Patient 3

A 65-year-old woman, with a history of nonspecific interstitial pneumonitis and pulmonary fibrosis and with documented *Mycobacterium avium* complex (MAC) on repeated sputum cultures since 2003, was admitted in March 2006 with increasing dyspnea and respiratory failure (Figure 3). Prior to admission she had multiple sputum cultures

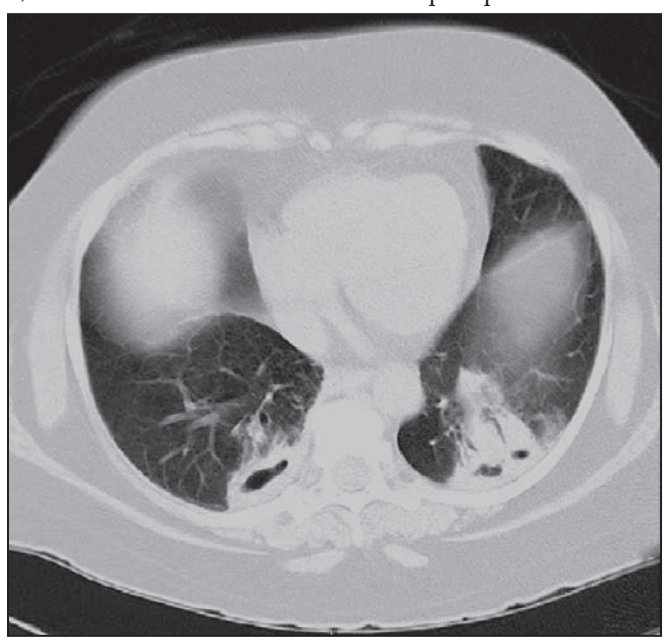

Figure 3. Axial computed tomogram of the chest in patient 3 showing bilateral cavitary focal disease with underlying fibrosis.

which were positive for growth of MAC and sensitive only to high dose clarithromycin, ethambutol, and rifabutin, with which she was treated for 18 months. Due to concomitant and repeated growth of methicillin-resistant *Staphylococcus aureus* (MRSA), she was also given linezolid intermittently. She was admitted to the hospital and treated empirically with broad-spectrum antibiotics while her MAC treatment was continued due to persistently positive sputum cultures. She failed to respond to therapy and died after a month of hospitalization secondary to progressive respiratory failure.

Patient 4

A 50-year-old man with severe chronic obstructive pulmonary disease (COPD) and bronchiectasis was on long term treatment for *Mycobacterium avium* complex pulmonary disease (MAC-PD) initially and later for macrolide-resistant MAC (MRMAC). He was admitted in moderately severe respiratory distress with fever and increasing cough. In addition to the multiple drugs used for the treatment of this patient throughout the course of his illness, therapeutic trials of thalidomide, interferon gamma, and high-dose mefloquine were given. Due to bilateral disease and poor pulmonary 4 function, surgery was not considered (Figure 4). The patient later died of respiratory failure and overwhelming infection.

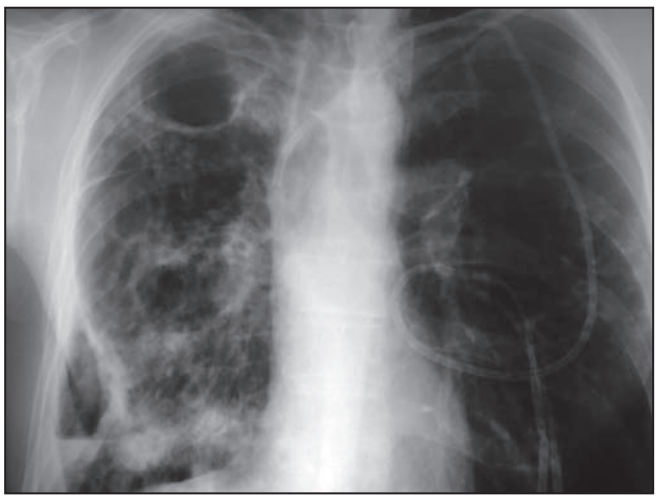

Figure 4. Postero-anterior chest radiograph in patient 4 reveals extensive bilateral disease.

Patient 5

A 42-year-old man with history of treated tuberculosis in 1980 developed fibrocavitary MAC infection in 1993. His treatment with ethambutol, rifabutin, and clarithromycin was erratic due to non-adherence. He was admitted to the hospital in March 2004 with increasing cough, night sweats, and a ten-pound weight loss. No culture and sensitivity data were available. With the history of erratic treatment, presumed macrolide resistance, and unilateral fibrocavitary disease, he was evaluated for surgical excision and pneumonectomy (Figure 5). His pulmonary function tests revealed a FEV1 of 1.4 L and a split perfusion pulmonary scan showed one percent perfusion of the right lung and 99% of blood flow to the left lung. The patient had a complicated operative and perioperative course and died of respiratory failure after a month-long stay in the intensive care unit (ICU).

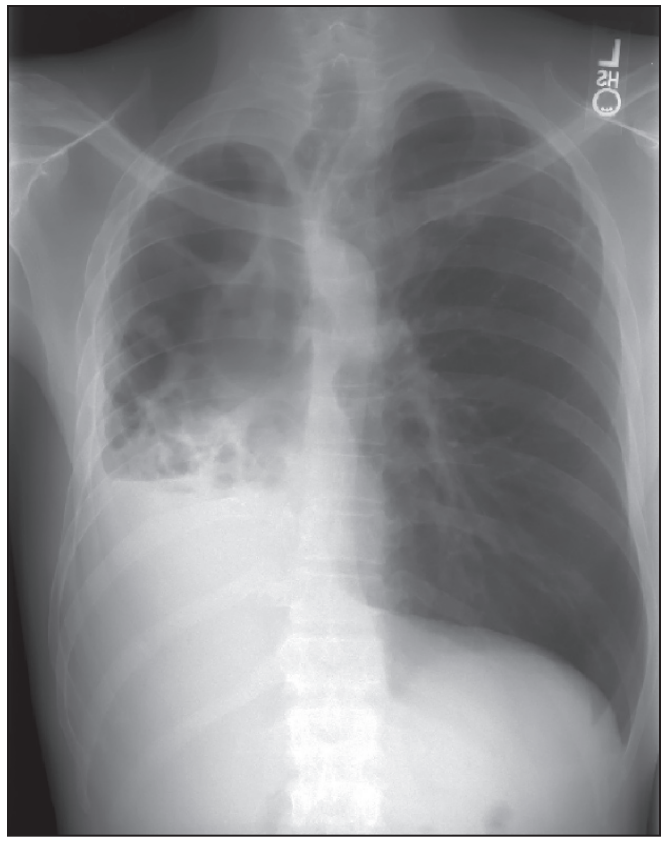

Figure 5. Postero-anterior chest radiograph in patient 5 shows underlying chronic obstructive pulmonary disease with severe volume loss and fibrocavitary disease in the right lung.

INTRODUCTION

Chronic pulmonary disease is the most common clinical manifestation of nontuberculous mycobacteria (NTM), and amongst this group *Mycobacterium avium* complex is becoming increasingly recognized as one of the most common mycobacterial pathogens in humans. *Mycobacterium avium* complex (MAC) organisms have been found to colonize natural water sources, indoor water systems, pools, hot tubs, and hospital water supplies.[1,2] MAC has long been known to cause serious disease in those with human immunodeficiency virus (HIV) infection, where it typically presents as disseminated disease. It is well recognized as a significant cause of pulmonary disease even in those with intact immunity. Although it has not been

clearly shown, inhalation from the environment is the likely mode of transmission in pulmonary MAC. Person-to-person spread does not seem to play a role.[3] It is not clear, however, why so few people become sick when exposure is so prevalent. Immunogenetic susceptibility and development of pulmonary MAC infection have been associated with specific human leukocyte antigen (HLA) phenotypes.[4] Defects in local pulmonary defense mechanisms, such as abnormal clearance of airway secretions, may play a role.

DISCUSSION

Pulmonary disease caused by MAC may take on one of several clinically different forms, ranging from asymptomatic colonization or persistent minimal infection, endobronchial involvement, progressive pulmonary disease with radiographic deterioration, hypersensitivity pneumonitis, or persistent overwhelming mycobacterial growth, often in a lung with underlying damage due either to chronic obstructive lung disease or to pulmonary fibrosis. The signs and symptoms of MAC-associated pulmonary disease are variable and may include chronic or recurring cough, sputum production, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain, and weight loss. Evaluation is often complicated by symptoms caused by coexisting lung diseases, such as bronchiectasis, chronic obstructive airway disease, or pulmonary fibrosis.

Physical findings are nonspecific, and chest ausculatory findings include rhonchi, crackles, wheezes, and squeaks, depending upon underlying disease and the presence of bronchiolitis and bronchiectasis. Patients with hypersensitivity pneumonitis may present with wheezing and cough. Those patients with nodular/bronchiectatic MAC disease tend to be postmenopausal women, many of whom have a characteristic morphotype with a thin body habitus; they may also have scoliosis, pectus excavatum, and mitral valve prolapse.[10]

The traditionally recognized patient with MAC lung disease is a male smoker in his fifth or sixth decade of life with a chest radiograph showing apical fibrocavitary lung disease. If left untreated, this form of disease is generally progressive within one to two years and can result in extensive cavitary lung destruction and respiratory failure.[11] MAC lung disease may also present radiographically with nodular and interstitial nodular infiltrates, frequently involving the right middle lobe or lingula, predominantly in postmenopausal, nonsmoking, white women,[12] such as patient # 1. This form of disease, known as Lady Windemere Syndrome, tends to have a much slower progression than cavitary disease. Even with this more indolent form of disease, progression can occur. In these cases, a high resolution scan may show findings that include multiple small peripheral pulmonary nodules centered on the bronchovascular tree and peripheral tubular or cylindrical bronchiectasis. The radiographic term tree-in-bud has been used to describe what may reflect inflammatory changes including bronchiolitis. Radiographic evidence of bullae and bullitis may be present, although pleural disease is not common. These patients may also have other pathogens isolated from culture, including *Pseudomonas aeruginosa*, *Staphylococcus aureus* and occasionally other NTM such as *M. abscessus* or *M. chelonei*.

Considering the relatively high numbers and wide diversity of *M. avium* and *M. intracellulare* in the environment, it is not surprising that some patients are infected by more than a single strain. However, a single strain of MAC tends to persist in patients with advanced fibrocavitary disease, whereas patients with fibronodular bronchiectasis may grow different strains over time, suggesting a susceptibility to the organism that allows re-infection after it has been eradicated.[13]

A recent statement by the American Thoracic Society and the Infectious Disease Society of America has suggested diagnostic criteria for NTM lung disease and proposed treatment protocols for various forms of MAC-PD.[5] Based on studies suggesting that macrolides are the only agents used for treatment of MAC disease for which there is a correlation between in vitro susceptibility, in vivo (clinical) response,[6] and their immune-modulating effects,[7] macrolide-containing treatment regimens have demonstrated beneficial effects and utility in management of MAC infection. Among patients who complete at least 6 months of macrolide-based therapy, about 55%-65% met the treatment success criterion of 12 months of sputum culture negativity while on therapy. The standard recommended treatment for most patients with macrolide-sensitive MAC is a regimen of clarithromycin or azithromycin, rifampin, and ethambutol. Amikacin may be added in some cases in the initial phase of the treatment.[5] Some patients may better tolerate a modified daily regimen. Once specific drug combinations are decided, some experts recommend a "step-ladder" approach to initiation of therapy with gradual but steady addition of one drug at a time.[5] This approach is adapted to ensure better drug tolerance and avoid potential early non-adherence to therapy. There is no data supporting the advantage of azithromycin over clarithromycin, but clinical observation suggests that the former is better tolerated by most patients. Similarly, while there is evidence of better in vitro sensitivity of MAC to rifabutin,[8] it does not have any superiority over rifampin. It is strongly recommended that macrolides not be used as monotherapy in order to prevent emergence of resistance.[5] Experts believe that because of frequent and severe adverse drug reactions, especially in elderly frail patients with poor tolerance to therapy, compromised renal function, and co-morbid conditions, complete microbiological cure may not always be possible. In these cases, given the indolent nature of MAC infection, an alternate approach with a two-drug "suppressive" regimen may be more beneficial and safe for the patient. However, there is no specific evidence to support this approach. It is reasonable to follow these patients clinically, radiographically, and microbiologically, with serial cultures and colony counts. It may be prudent to categorize patients as "colonizers" or "persisters" in which case bronchial toilet may be the best approach,

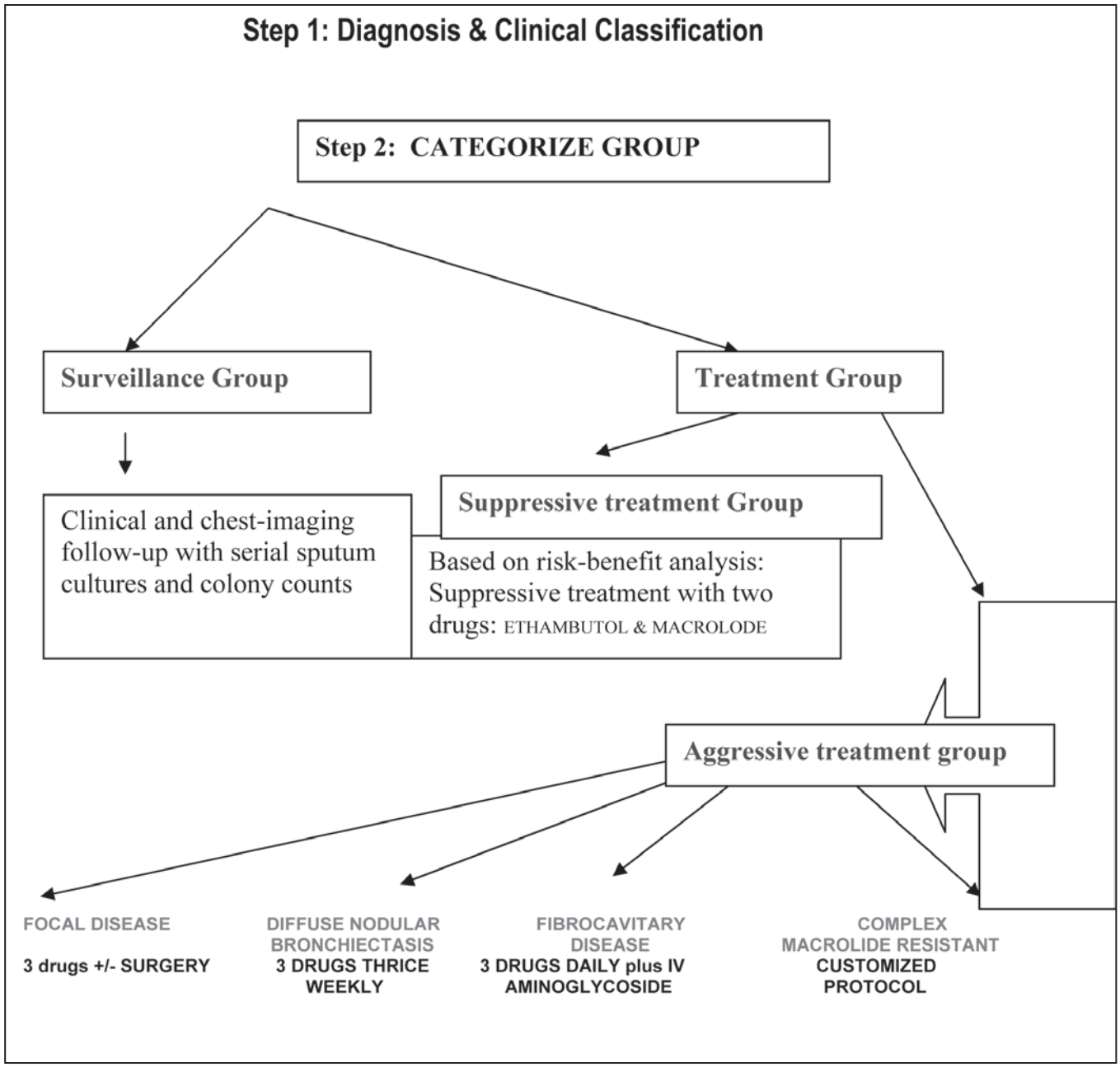

Figure 6. Management algorithm for *Mycobacterium avium* complex pulmonary disease.[5,9]

versus "mild disease" where the benefit of suppressive therapy may far outweigh the risks and dangers of long term aggressive therapy, or as "severe disease" where customized aggressive therapy is indicated.[5,9] General measures focusing on the management of bronchiectasis include postural drainage, mucus clearance, smoking cessation and enhanced nutritional support.

These measures should be adopted and supplemented with broad-spectrum non-macrolide antibiotics as needed to target bacterial super-infection. Based on these observations and a previously published, proposed clinical classification,[9] an algorithmic approach is outlined (Figure 6).

Patients are considered treatment failures if they have not had a response (microbiologic, clinical, or radiographic) after six months of appropriate therapy or achieved conversion of sputum to culture negative after 12 months of appropriate therapy.[5] Multiple factors can interfere with the successful treatment of MAC lung disease, including medication non-adherence, medication side effects or intolerance, lack of response to a medication regimen, or the emergence of a macrolide-resistant strain. Treatment failure may also be due to failure to convert sputum cultures to negative because of poor drug penetration into the damaged lung tissue with sub-therapeutic tissue levels or

due to drug-drug interactions leading to suboptimal drug levels. In addition, factors identified as contributing to the poor response to therapy include poor compliance, cavitary disease, previous treatment for MAC lung disease, as in case patient #5, and a history of chronic obstructive lung disease or bronchiectasis.[14] Most cases of treatment failure can be attributed to MAC isolates that are resistant to macrolides.[15] Among the alternate drugs, moxifloxacin, as compared to other fluoroquinolones, appears to have a much more favorable in vitro and in vivo animal model profile.[16] Clinical experience has proven that it is better tolerated by the patients as compared to other alternative medications. Also, moxifloxacin has been shown to achieve very high levels in human alveolar macrophages and lung epithelial lining fluid, which may facilitate clinical effectiveness.[16] Although MAC has historically been universally susceptible to clofazimine, its use and efficacy has been disappointing in the clinical setting.[17] The data on linezolid are preliminary,[18, 19] and clinical experience with this agent for treatment of MAC is limited. Cycloserine, ethionamide, and isoniazid have all been evaluated for treatment of MAC, but resistance is common.[15] Mefloquine, an antimalarial agent, has also been studied,[20, 21] and although human studies are lacking, animal and in vitro data show that mefloquine is bactericidal against both clarithromycin-sensitive and clarithromycin-resistant MAC strains.[21] The mechanism of action is not clear though it has been suggested that, based on its effect on *Plasmodium falciparum*, mefloquine may have some effect on the cell membranes of MAC organisms.[21] This agent was tried in patient #4 and was well tolerated. Unfortunately evidence of efficacy was lacking, perhaps due to the advanced state of the patient's disease.

The role of immune modulator therapy, specifically IFN-γ, in mycobacterial disease has also been studied.[22, 23] The review of data from a recent large multicenter trial of inhaled IFN-γ adjunct therapy for pulmonary MAC infection appears to demonstrate no added benefit when this therapy is included in a macrolide-based three-drug treatment regimen.[14] The clinical efficacy of thalidomide, a TNF-α inhibitor, especially in cachectic patients with MAC, is controversial.[24, 25]

Strategies for patients failing medical therapy include surgery, along with the use of anti-MAC antibiotics based on the mycobacterial sensitivity results. When present, localized disease lends itself best to surgical intervention. Predictably, those that have poor preoperative lung function do less well, and postoperative complications, especially with a right sided pneumonectomy, tend to occur more frequently.[26-28] To date, no controlled surgical trials for MAC lung disease have been published. There are no established criteria for patient selection for surgical therapy of MAC-PD, and there are potentially severe perioperative complications and few centers with extensive experience. Resection of a solitary pulmonary nodule due to MAC, in addition to concomitant antimycobacterial treatment, is recommended by some experts because it is well tolerated and may provide a cure without the prolonged treatment and its associated problems. Surgical resection of limited (focal) disease, in a patient with adequate cardiopulmonary reserve who can withstand partial or complete lung resection, in combination with multi-drug treatment regimens can be successful and lead to early sputum conversion.

CONCLUSION

MAC, which is ubiquitous in our environment, has protean manifestations especially in those with no recognizable immune impairments. Drug treatment, however, remains difficult, secondary to medication side effects and high failure rates. Management strategies must be individualized based on the degree of involvement, the goal of therapy, and the risk-benefit ratio. This review and case series underscores the importance of categorizing patients in groups who may require either close surveillance and no specific antimicrobial therapy, or suppressive two-drug therapy, or more aggressive treatments. It also highlights the often unrecognized morbidity and mortality of severe progressive MAC-PD and the need for increased awareness of MDRMAC.

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CME QUESTIONS

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Choose the answer that is most correct for each question.

1. True/False
   Although it has long been known to cause serious disease in those with human immunodeficiency virus (HIV) infection, *Mycobacterium avium* complex is well recognized as a significant cause of pulmonary disease even in those with an intact immune system.

2. True/False
   The standard recommended treatment for most patients is a three-times-weekly regimen of clarithromycin or azithromycin, rifampin, and ethambutol with or without amikacin.

3. The clinical presentations of *Mycobacterium avium* complex pulmonary disease include
   a. Asymptomatic colonization or persistent minimal infection.
   b. Endobronchial involvement.
   c. Progressive pulmonary disease with radiographic deterioration.
   d. Hypersensitivity pneumonitis.
   e. All of the above.

4. Most cases of treatment failure can be attributed to MAC isolates that are resistant to
   a. Macrolides.
   b. Ethambutol.
   c. Rifampin.
   d. Isoniazid.
   e. All of the above.