Journal of the Formosan Medical Association (2020) 119, S67—S75

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

Review Article

Treatment for *Mycobacterium avium* complex lung disease

Sheng-Wei Pan [a,b,c], **Chin-Chung Shu** [d,e], **Jia-Yih Feng** [a,b], **Wei-Juin Su** [a,b,*]

[a] *Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Institute of Public Health, National Yang-Ming University, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[e] *College of Medicine, National Taiwan University, Taipei, Taiwan*

Received 9 March 2020; received in revised form 4 May 2020; accepted 5 May 2020

KEYWORDS
Disease progression;
Mycobacterium avium complex Lung disease;
Nontuberculous mycobacterium;
Treatment

Mycobacterium avium complex (MAC) is the major pathologic nontuberculous mycobacteria causing lung disease (LD) in humans worldwide. Although the burden of MAC-LD has increased over the past two decades, treatment remains difficult because of intolerance of long-term antibiotics, lack of adherence to guidelines, and disease recurrence. The current guidelines recommend antibiotic initiation for patients with MAC-LD and severe disease and in those with disease progression. Thus, physicians should consider antibiotic treatment for patients with MAC-LD and cavitary pulmonary lesions or symptomatic non-cavitary nodular bronchiectasis pattern at initial visits and also for those with clinical deterioration during follow-up. The standard three-drug regimen should be macrolide, rifamycin, and ethambutol. Physicians should monitor side effects in patients and maintain the regimen for 12 months, beginning from when sputum conversion has been obtained. With adherence to guideline-based therapy, treatment is successful in two thirds of treatment-naïve patients without macrolide resistance. Without adherence, macrolide resistance can occur, which leads to poor outcomes in patients with MAC-LD. Although the discovery of new treatment options is warranted, adherence to guidelines remains most crucial in treating patients with MAC-LD. It is worth mentioning that the majority of current recommendations are based on observational studies or small-scale clinical trials.

* Corresponding author. Department of Chest Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Taipei, Taiwan.
E-mail addresses: sanweipan@gmail.com (S.-W. Pan), ccshu@ntu.edu.tw (C.-C. Shu), peterofeng@gmail.com (J.-Y. Feng), wjsu.mail@gmail.com (W.-J. Su).

https://doi.org/10.1016/j.jfma.2020.05.006

Introduction

Nontuberculous mycobacterium (NTM) consist of more than 170 species and can cause progressive lung disease (LD) in both immune-compromised and immune-competent individuals.[1,2] The incidence of NTM-LD has increased worldwide over the past two decades.[3–6] Regarding the causative species, *Mycobacterium avium* complex (MAC) is the major species in most areas of the world, particularly East Asia, North America; it comprises 27%—85% of pathogens of NTM-LD.[7–10] Similarly, the most prevalent NTM in Taiwan is also MAC (41.5%), although one epidemiologic study found that MAC dominates in northern Taiwan but MAC and *Mycobacterium abscessus* are both dominant in southern Taiwan, suggesting a regional difference in the pathogenic NTM species.[6,7]

Among MAC species, *M. avium* and *Mycobacterium intracellulare* are the two major subspecies, with the latter being more virulent.[11] Using genetic methods, the novel *Mycobacterium chimaera* was first distinguished from *M. intracellulare* after 2004.[12] Of the remaining rare subspecies, *Mycobacterium colombiense*, *Mycobacterium marseillense*, *Mycobacterium timonense*, and *Mycobacterium yongonense* are less virulent and less likely to cause MAC-LD.[13] Interestingly, MAC-LD caused by *M. chimaera* is relatively rare in South Korea, but up to 28% of cases of MAC-LD was reportedly caused by *M. chimaera* in the United States.[13] Recently, a MAC-LD report from Taiwan revealed that the percentages of *M. intracellulare*, *M. avium*, *M. chimaera*, and other subspecies were 33%, 39%, 15%, and 12%, respectively, suggesting that *M. chimaera* and other subspecies were not uncommon.[14]

Patients with MAC-LD usually present with indolent disease courses and may be stable for years.[15] However, in a cohort study of patients with MAC-LD, the 5-year mortality rate was 22.2% for patients who underwent treatment but 33.3% for patients who did not.[16] Nevertheless, determining the appropriate timing of antibiotic therapy initiation in patients with NTM-LD is challenging.[2] In addition, even when treatment was considered, the long-term course and adverse effects of antibiotics were barriers to physicians' and patients' adherence to the clinical consensus.[5,10] Thus, considering the increasing burden of MAC-LD and the challenge of its therapy, we review treatment strategies for MAC-LD in this report. However, it is worth noting that the majority of scientific suggestions stated in this review and recommendations proposed by current guidelines are based on low level evidence studies, including observational studies or small-scale clinical trials.

Disease course and predictors of progressive disease

According to the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) 2007 statement on the diagnosis of NTM disease, NTM-LD is defined by 1) compatible respiratory symptoms, 2) typical radiographic findings, and 3) the microbiologic criteria of two sputum acid-fast bacilli (AFB) cultures positive for NTM, one bronchoscopic AFB culture positive for NTM, or one lung biopsy with compatible pathology plus one positive culture; NTM-LD can only be diagnosed if other diagnoses are justifiably excluded.[17] In 2015, Boyle et al. evaluated 436 patients with pulmonary isolate culture positive for MAC in the United States and determined 57.6% of them to have had MAC-LD.[13] Low body mass index (BMI), chronic obstructive pulmonary disease (COPD), AFB smear positivity, harboring *M. avium* or *M. intracellulare* subspecies as opposed to *M. chimaera*, cavitary disease, and bilateral lung disease were predictors of meeting the diagnostic criteria of NTM-LD. This report confirms the significance of host characteristics and microbiologic and radiographic indicators when diagnosing MAC-LD. In the subsequent paragraphs, we review the indicators potentially associated with the radiographic progression, disease progression, and microbiologic persistence of MAC-LD.

First, several microbiologic factors are associated with the radiographic progression of MAC-LD, as generally defined by new pulmonary lesions or cavitary formation. Regarding bacterial load, the number of MAC-positive sputum cultures is strongly associated with the activity of a pulmonary lesion. A classic Japanese study reported that 90% and 98% of patients with two and three MAC isolates, respectively, had a cavitary lesion, but only 2% of patients with one isolate did.[18] Recently, Huang et al. conducted a survey of Taiwanese patients with bronchoscopy-diagnosed NTM-LD and negative sputum cultures and noted that 55% of the etiologic NTM were MAC isolates.[19] Interestingly, although a single bronchoscopic AFB culture being positive for NTM satisfies the ATS/IDSA microbiologic criterion, only 28% of initially untreated cases in that study had radiographic progression within 2 years. Furthermore, suggesting the importance of bacterial load, that study noted that an acid-fast smear grade $\geq$2 in bronchoscopic samples is an independent predictor of radiographic progression.

Second, initial radiographic findings are also related to radiographic progression of MAC-LD. There are two typical radiographic patterns in MAC-LD, namely the nodular bronchiectatic (NB) and fibrocavitary forms.[17] Patients with the NB pattern usually experience bronchiectatic changes, tree-in-bud opacities and nodular lesions in the right middle lobe or lingular lobe of left upper lung. Inflammatory changes including bronchiolitis may progress and can even result in cavitation of the nodules (Figs. 1—3). Patients with NB pattern are generally thin and older-adult women with no smoking history. By contrast, fibrocavitary lesions in patients with MAC-LD are mostly located in the apical lung area, a finding similar to the radiographic findings in cases of pulmonary tuberculosis (Fig. 4). Patients with fibrocavitary lesion are usually older-adult men with a smoking history and high bacterial burden. Because of inflammation and destruction of their lungs, patients with MAC-LD who present both radiographic changes can have cough, sputum production, and hemoptysis as well as constitutional symptoms such as weight loss and night sweating.[2]

Notably, patients with MAC-LD and a fibrocavitary pattern have a more aggressive disease course and may require early antibiotic initiation. Ito et al. investigated MAC-LD in Japan and discovered that predictors of mortality included no anti-MAC treatment and also the presence of cavitary lesions.[16] In a MAC-LD cohort study conducted in South Korea, Koh et al. reported that although the time between diagnosis and antibiotic treatment was relatively long at approximately 5.8—7.0 years for patients

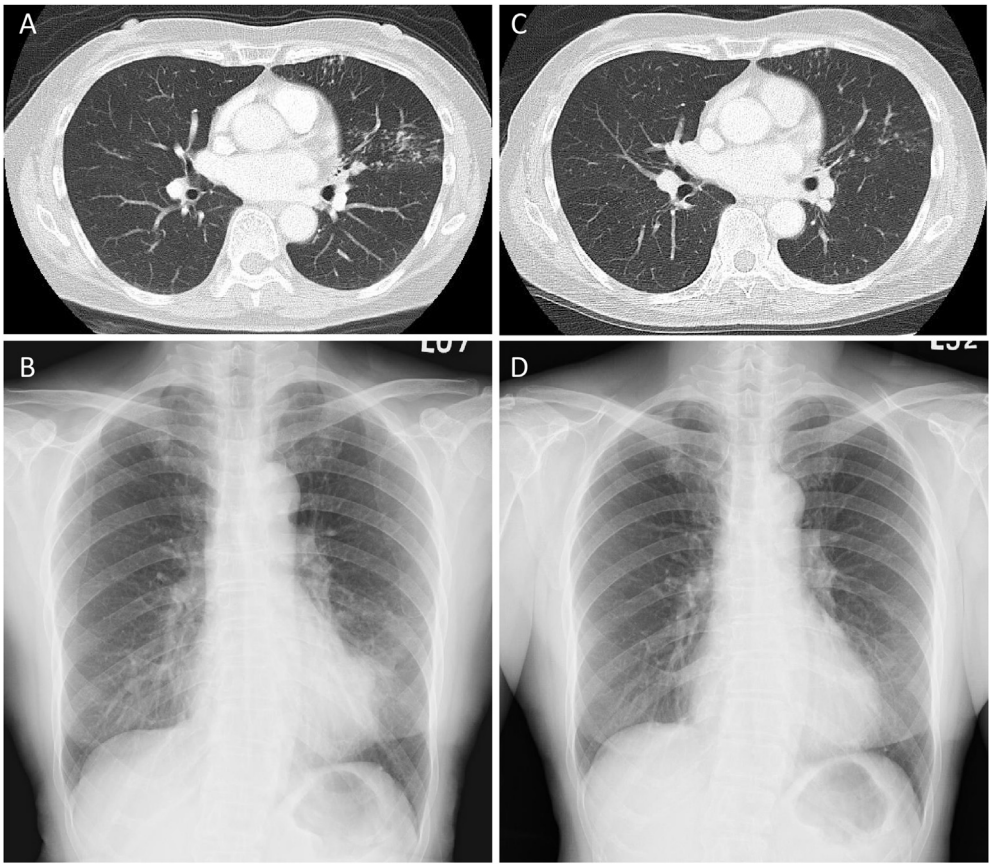

Fig. 1 Non-cavitary nodular bronchiectatic pulmonary lesions in a 68-year-old woman with initial presentation of productive cough and hemoptysis lasting weeks. Her sputum samples were AFB culture positive for *Mycobacterium avium* complex (MAC). (A) Chest computed tomography (CT) reveals multiple small nodules, tree-in-bud lesions, and mild bronchiectasis in the lingular segment of the left upper lobe. (B) Plain chest radiograph indicates patchy consolidation in the lingular segment, consistent with peri-bronchiectatic inflammation. (C) Chest CT indicates that 7 months of three-times-weekly anti-MAC therapy with clarithromycin, ethambutol, and rifampin results in decreased extent of the tree-in-bud and nodular lesions. (D) Corresponding chest radiograph reveals improvement of consolidation in the lingular segment of the left upper lobe. Her symptoms improved and sputum samples were culture negative for MAC.

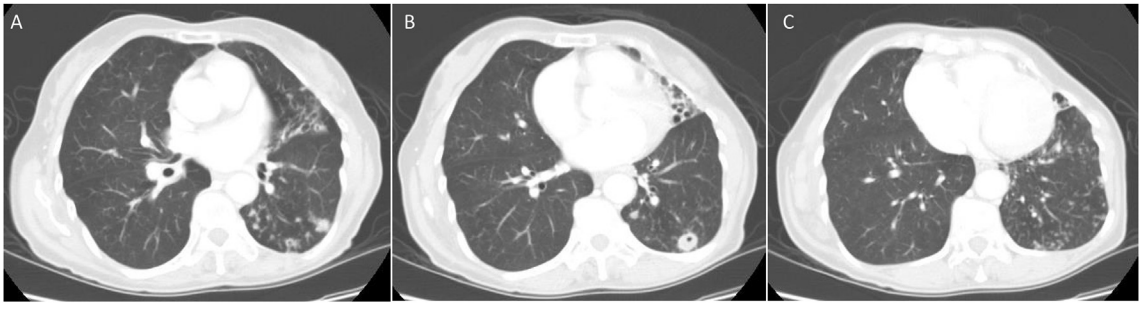

Fig. 2 Cavitary nodular bronchiectatic radiographic pattern in a 64-year-old woman with MAC—lung disease (LD). Her symptoms included sputum production, which had been ongoing for years, and the sputum samples were AFB culture positive for MAC. Compared with previous images, chest CT reveals persistent bronchiectasis in the lingular segment of the left upper lobe and increased number and size of nodules and tree-in-bud lesions in the left lower lobe of the lungs (A—C). Some enlarged nodules in the left lower lobe developed cavitation, suggesting the aggressive nature of the MAC-LD in this patient (A, B).

with an NB pattern, it could be as short as 1.5 years for those with fibrocavitary lesions.[20] In another South Korea cohort study on untreated patients with NB-form MAC-LD, after a mean follow-up of 3 years, only 48% of them had clinical deterioration with worsening symptoms or radiologic progression.[21] Thus, patients with NB-form MAC-LD may have a favorable indolent course that benefits from symptom management without antibiotic initiation.

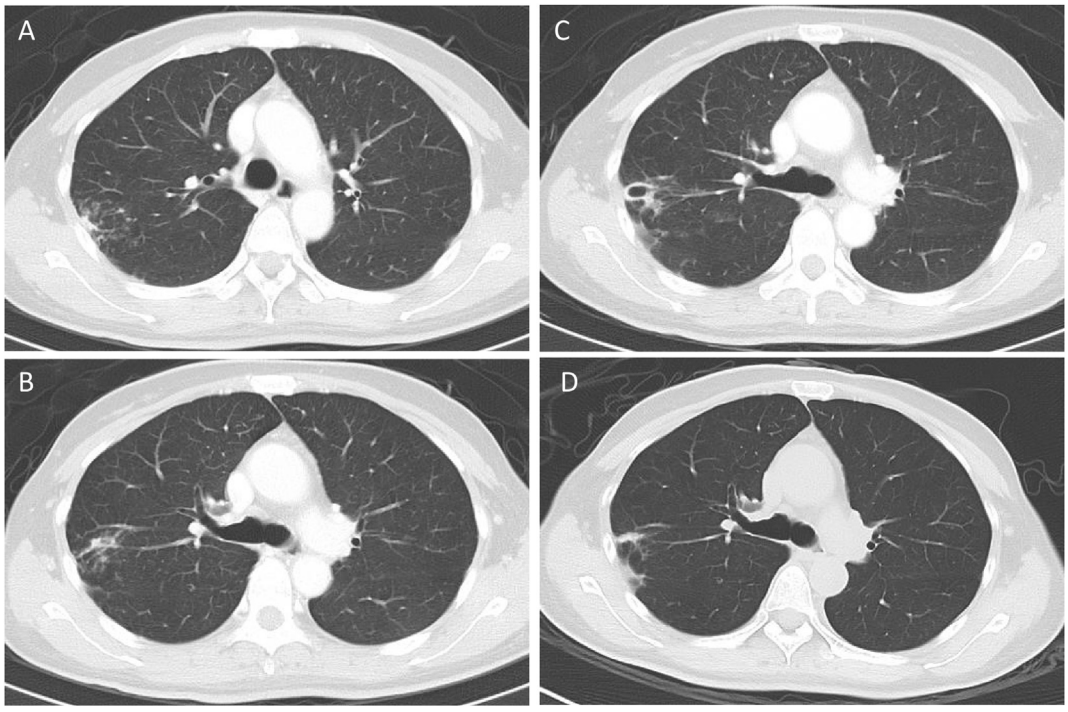

Fig. 3 Progressive pulmonary cavity formation over nodular bronchiectatic (NB) area, namely cavitary NB pattern, in a 51-year-old woman with minimal symptoms under regular radiographic follow-up. Her sputum samples were AFB smear positive and culture positive for MAC at the time of cavity formation. (A) Three years before this presentation, chest CT reveals tree-in-bud lesions in the right upper lobe. (B) There were also minimal fibrotic changes at a slightly lower level of the NB area, suggesting repeated inflammation. (C) Presentation chest CT at the same level as (B) discloses a newly developed right upper lobe cavity. (D) Chest CT after 6 months of daily anti-MAC therapy with azithromycin, ethambutol, and rifampin demonstrates regression of tree-in-bud lesions and near resolution of the cavity in right upper lobe.

Recently, several researchers have noted the importance of cavitary formation in patients with MAC-LD of the NB form. Kitada et al. investigated the outcomes of such patients in Japan (61% receiving treatment) and observed that 22% and 53% of them developed radiographic deterioration after 5 and 10 years of follow-up, respectively.[22] Notably in that study, 13.9% of the patients with NB-form MAC-LD had superimposed cavitary lesion at their initial visit, which was associated with radiographic deterioration. By the recent definition, cavitary NB pattern was defined as cavities formation within nodules of NB lesions (Fig. 2).[23] Koh et al. assessed the phenotype of 481 treatment-naïve patients with MAC-LD and discovered that 25% of the patients had fibrocavitary disease, 58% had non-cavitary NB disease, and 17% had cavitary NB disease. Both the fibrocavitary and cavitary NB groups had a less favorable outcome than the non-cavitary NB group did,[20] suggesting that the patients with cavitary NB forms had aggressive disease leading to cavitary formation and poor outcomes.

Unlike studies detecting radiographic progression alone, several retrospective studies have investigated the disease progression of MAC-LD as defined by initiation of antibiotic treatment for MAC or radiographic progression. In a South Korean study involving 590 patients with MAC-LD, fibrocavitary pattern, sputum AFB smear positivity, age $\leq$60 years, and *M. intracellulare* as opposed to *M. avium* were significant predictors of disease progression requiring antibiotic initiation.[11] The cumulative rates of antibiotic initiation within 2 years in patients harboring *M avium* and *M intracellulare* were 42% and 58%, respectively. In another Korean study, 62.5% of 488 patients with MAC-LD had progressive disease that resulted in antibiotic initiation within 3 years. Sputum AFB smear positivity, fibrocavitary type, and more extensive radiological disease were associated with progressive disease.[15]

Crucially, for patients with stable MAC-LD, spontaneous sputum culture conversion may occur. Hwang et al. reported that among 93 treatment-naïve patients with stable MAC-LD for 3 years, spontaneous sputum conversion occurred in 51.6% of them. The predictors of sputum conversion were young age, high BMI, and initial sputum AFB smear negativity.[15] Pan et al. observed 126 patients with MAC-LD in Taiwan and disclosed that 60% of them continued to have positive MAC cultures after the initial year and nearly half of them presented with radiographic progression. The independent predictors of persistent culture-positivity were low BMI, NB pattern, and high grade of AFB smear positivity. Crucially, persistent culture-positivity for MAC led to an elevated risk of radiographic progression in patients with MAC-LD.[24]

In summary, the risk factors of disease progression of MAC-LD are fibrocavitary lesions, extensive disease, AFB smear positivity, *M. intracellulare* subspecies, and persistent culture-positivity. This information may help physicians identify patients with MAC-LD at increased risk of poor outcomes who may benefit from antibiotic initiation,

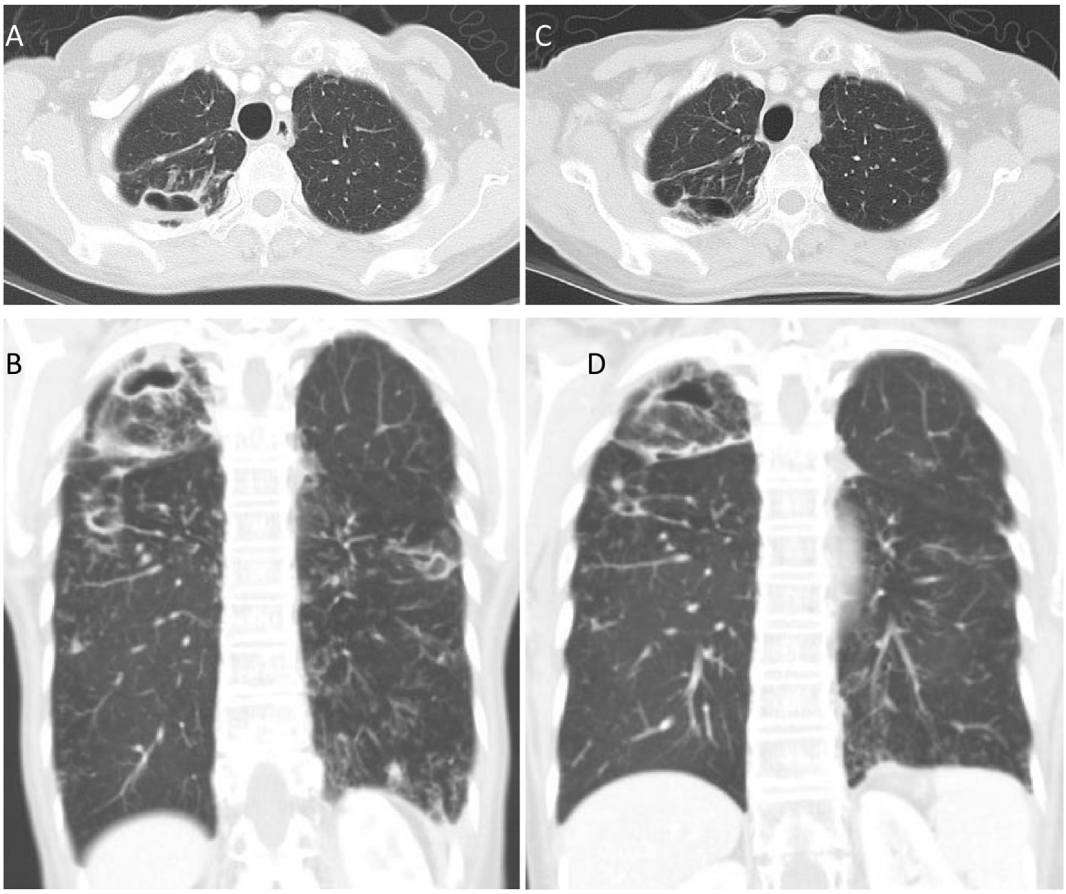

Fig. 4 Fibrocavitary lung lesions in a 70-year-old woman with intermittent hemoptysis and progressive body weight loss over 6 months. Her sputum samples were AFB smear positive and culture positive for MAC. (A) Chest CT shows cavitation with subpleural thickening and patches of fibrotic change in the right upper lung. (B) In addition, CT scan discloses volume reduction of the right upper lobe and bronchiectasis in left lower lobe. (C, D) After daily anti-MAC therapy with oral azithromycin, ethambutol, and rifampin for 12 months and parenteral amikacin in the initial 2 months, chest CT reveals improvement of the cavitary lesion and nodular inflammation over bilateral lung fields.

although such clinical decision making generally remains complex.

Patient management and decision to treat MAC-LD

Making the diagnosis of NTM-LD itself does not necessitate the initiation of antibiotic therapy; the decision for such initiation depends on an individualized assessment of the benefits and potential risks in a patient with MAC-LD.[17] According to the 2017 British Thoracic Society (BTS) guideline for the management of NTM-LD, antibiotic initiation should be considered for patients with severe NTM-LD and for those with clinical deterioration or disease progression.[2] Thus, for patients who have MAC-LD with minimal symptoms, non-extensive radiographic changes, and low bacterial load, a favorable strategy is to attempt symptomatic treatment first and continue clinical observation in initial visits.

The clinical worsening of respiratory symptoms in patients with MAC-LD may not be due to MAC infection itself. These patients may experience symptoms due to underlying bronchiectasis and COPD, which may improve with targeted treatment.[25] To ensure pulmonary hygiene, patients with MAC-LD and sputum impaction may benefit from non-pharmacological management including chest percussion and postural drainage as well as mucolytic agents.[26] Patients with MAC-LD and COPD may experience symptom improvement after bronchodilator inhalation.[27]

However, symptom management cannot stop an aggressive disease course in MAC-LD with fibrocavitary lesions.[20] In patients with cavitary lesions, even those with a cavitary NB pattern, the risks of disease progression and unfavorable outcomes are increased.[20,22] Thus, early treatment should be considered in patients with cavitary lesions. By contrast, patients with non-cavitary NB pattern tend to have lower risk of disease progression and may be stable without antibiotic initiation.[20] However, if patients with non-cavitary NB pattern deteriorate and have worsening symptoms, an increased bacterial burden, or radiographic progression, a physician should consider antibiotic treatment to slow the progression of MAC-LD.[2]

Other host characteristics correlated with poor outcomes before antibiotic treatment in patients with MAC-LD have been old age, low BMI, and persistent culture-positivity.[15,24] In addition, one post-marketing survey found

that using anti-tumor necrosis factor (TNF)-α agents was correlated with an increased risk of developing NTM diseases. Of note, infliximab was the most commonly implicated anti-TNF-α drug (70%) whereas *M. avium* was the predominant causative pathogen (50%).[28] Therefore, the BTS guideline also recommends to consider offering antibiotic treatment for NTM-LD patients taking TNF-α inhibitors.[2]

The potential indicators for initiation of anti-MAC treatment are summarized in Table 1. Critically, the decision to initiate anti-MAC therapy should be based on the combination of these indicators and an individualized assessment of the benefits and risks of treatment.

Antibiotic treatment and clinical consideration

According to the ATS/IDSA guideline, the standard three-drug regimen for MAC-LD is macrolide (azithromycin or clarithromycin), rifamycin (rifampicin or rifabutin), and ethambutol.[17] For severe cases, it is recommended that parenteral aminoglycoside (streptomycin or amikacin) injection is added for a duration of 2—3 months in the initial treatment stage. The oral three-drug regimen should be continued for an additional ≥12 months after the time of sputum conversion, which is defined as the date of the first of three consecutive negative sputum cultures over a minimum period of 3 months. The following are several precise considerations in MAC-LD treatment.

First, patients with MAC-LD presenting with NB lesions and minimal symptoms may initially be given symptomatic treatment.[2] However, if the symptoms worsen despite such management, three-drug antibiotic therapy should be considered. Per the guideline, an intermittent or three-times-weekly (TIW) regimen is recommended for patients with MAC-LD and NB pattern but without severe or previously treated disease.[17] In a retrospective cohort study of 217 treatment-naïve patients with MAC-LD and non-cavitary NB pattern, Jeong et al. disclosed that the TIW therapy group had less modification of the initial antibiotic therapy than the daily group did (21% vs. 46%; $p < 0.001$).[29] Importantly, the TIW and daily groups had similar rates of symptomatic improvement, radiographic improvement, and sputum culture conversion. Accordingly, this study concluded that the TIW regimen is a reasonable initial treatment for patients with MAC-LD presenting with non-cavitary NB radiographic pattern.[29] Fig. 1 details the radiographic changes of a symptomatic patient with MAC-LD and non-cavitary NB lesions before and during three-drug-regimen TIW treatment.

Second, both the ATS/IDSA and BTS guidelines recommend that a patient with NB lesions and severe disease should receive a daily regimen but not intermittent TIW therapy.[2,17] Different from the ATS/IDSA guideline, which refers to severe disease as cavitary disease, the BTS guideline defines severe disease as not only cavitary lesions or severe infection but also AFB-smear-positive respiratory samples and severe systemic illness.[2] Thus, per the BTS guideline, a physician may consider daily therapy for patients with non-cavitary NB and AFB smear positivity. Regarding the unexplained small disparity between the guidelines,[30] we think that having AFB smear-positive samples alone does not necessitate the initiation of a daily regimen for patients with non-cavitary NB lesions. It warrants further research to construct more comprehensive methods to delicately assess disease severity in patient with MAC-LD.

Third, both the ATS/IDSA and BTS guidelines suggest that patients with MAC-LD and initial fibrocavitary lesion should receive antibiotic treatment. Notably, according to expert opinion in a 2019 publication, patients with cavitary NB pattern should be treated as are patients with fibrocavitary lesion, that is, with a daily regimen.[2,30] Fig. 3 presents images of cavitary formation in NB lesions before antibiotic treatment and its regression after treatment in a patient with MAC-LD.

Fourth, in patients with cavitary MAC-LD and extensive lung lesions or severe symptoms, an oral daily three-drug regimen with inclusion of parenteral aminoglycoside therapy for the initial 2 or 3 months is often recommended.[2] Fig. 4 presents the imaging results of a patient with MAC-LD and initial fibrocavitary pattern, with images obtained before and during daily oral antibiotic therapy in combination with amikacin administration. Finally, for patients with refractory MAC-LD, despite the available antibiotic therapies, surgical intervention should be considered if the pulmonary lesion is focal and severe.[2] The role of surgical intervention is discussed in another review article in the current issue of this journal.

In Table 2, matching the radiographic pattern and disease course with an appropriate antibiotic regimen, we

Table 1 Indicators for the initiation of treatment for *Mycobacterium avium* complex (MAC)—lung disease.

Indicators & timing	Patient related factors	Chest radiographic features	Microbiological features
At initial visits	Severe symptoms[a], low BMI, and immunocompromised conditions (on TNF-α inhibitors)	Fibrocavitary lesion, cavitary nodular bronchiectasis, and extensive involvement	AFB smear positive and virulent MAC subspecies
During follow-up	Worsening symptoms even on symptomatic therapy[a]	New or worsening lung cavitation, new foci of consolidation/tree-in-bud opacity, increased size/number of nodules, and worsening extent and/or severity of bronchiectasis	Persistent culture positivity, increase in grade of AFB smear positivity and number of positive MAC cultures

AFB, acid-fast bacilli; BMI, body mass index; TNF-α, tumor necrosis factor-α.
[a] Other diseases must be excluded as the cause of symptoms.

Table 2 Guideline-based therapy for treatment-naïve patients with MAC—lung disease.

Disease severity & image pattern	Mild symptoms	More symptoms or progression	Severe disease
Non-cavitary NB	Symptomatic treatment[a]	TIW three drugs[b]	Daily three drugs[c] ± AG injection[d]
Fibrocavitary or cavitary NB	Daily three drugs[c] ± AG injection[d]	Daily three drugs[c] + AG injection[d]	Daily three drugs[c] + AG injection[d] ± surgery

The three-drug regimen is macrolide, rifamycin, and ethambutol; AG, aminoglycoside; NB, nodular bronchiectasis; TIW, three-times-weekly.

[a] Including mucolytic agents, postural drainage, and bronchodilator if indicated.

[b] The three-times-weekly (TIW) regimen is 600 mg of rifampin TIW and 25 mg/kg ethambutol TIW as well as either 500 mg of azithromycin TIW or 1000 mg of clarithromycin TIW. Regarding drug—drug interactions, combining azithromycin with moxifloxacin, amiodarone or antiemetics can increased the risk of QTc prolongation. Since antacids reduce the absorption of azithromycin, patients may take antacids 2 h apart from that. While azithromycin increases digoxin levels, clarithromycin increases the concentrations of coumarins, theophylline, certain antiepileptics and antivirals. Thus, a physician may consult a pharmacist for these co-medications.

[c] The daily regimen is 250—500 mg azithromycin daily or 500—1000 mg of clarithromycin daily, 450—600 mg of rifampin or 150—300 mg/d of rifabutin (lower dose for weight $<$ 50 kg) daily, and 15 mg/kg ethambutol daily.

[d] The aminoglycoside (AG) regimen can be amikacin 15 mg/kg once daily or 15—25 mg/kg TIW intravenously or intramuscularly if tolerated.

present a modified therapeutic approach for treatment-naïve patients with MAC-LD. Importantly, three-drug therapy in different scenarios should be maintained for an additional $\geq$12 months after sputum culture conversion. Physicians should explain and monitor the side effects of antibiotics. The side effects include QTc prolongation associated with macrolide (particularly azithromycin), ototoxicity from macrolide and aminoglycoside, optic neuritis from ethambutol, hepatotoxicity from rifampicin and renal injury due to aminoglycoside. In addition to blood tests and audiometry, physicians should cautiously check electrocardiogram for patients using macrolide at baseline and 2 weeks after the addition of any medication that is known to prolong QTc (e.g., moxifloxacin, amiodarone, and antiemetics including domperidone, metoclopramide, and serotonin blockers).[2]

Drug sensitivity test and macrolide resistance

The current guidelines recommend routine identification of NTM species after the diagnosis of NTM-LD and an optional drug sensitivity test (DST) if a decision to treat is made. Although treatment regimens can be guided by the etiologic NTM species in most cases,[2,17] a physician should request a DST to confirm the appropriateness of a regimen. Among the DSTs for MAC-LD, data on macrolide and amikacin have been found to be generally necessary.[31,32] This is because *in vitro* DST results for macrolides and amikacin may be correlated with *in vivo* responses. By contrast, *in vitro* susceptibility to rifampin and ethambutol have shown poor correlations with clinical responses.[33]

Although the reasons for drug resistance in NTM remain unclear, two potential mechanisms exist: mutational resistance acquired during anti-MAC treatment and natural drug resistance.[25] Natural drug resistance in MAC and other bacteria may not be reflected in *in vitro* DST, resulting poor correlation between treatment response and the DST results. By contrast, acquired mutational resistance involving the 23S ribosomal RNA (rRNA) gene for macrolide and 16S rRNA gene for amikacin can be detected by a phenotypic DST. Poor adherence to standard combination therapy, an inadequate course, and inadequate companion medications for macrolides and amikacin may contribute to acquired mutational resistance to these drugs.[31]

In a Japanese study, the initial screening determined macrolide resistance in 18% of 565 patients with MAC-LD.[34] A report from Taiwan noted that 5% of 105 treatment-naïve patients with MAC-LD had 23S rRNA mutation, suggesting low incidence of macrolide resistance genotypes of MAC isolates.[14] Although sequencing methods for detecting mutation are an alternative strategy for assessing the macrolide resistance phenotypes of MAC, the genotyping method remains highly specific but lacking in sensitivity.[35]

As reported in a South Korean study, even after a median 33 months of guideline-based combination treatment, only 22% (16 of 72) patients with refractory MAC-LD developed macrolide resistance, with 80% of the resistant isolates exhibiting compatible mutation in the 23S rRNA gene. In addition, pre- and post-treatment genotyping revealed that 49% of the refractory MAC-LD cases had reinfection by new MAC strains and 24% by both original and new strains.[36] Thus, even on long-term treatment, macrolide resistance develops infrequently in MAC-LD when guideline-based combination therapy is adhered to. However, as noted in a Canadian report, more than half of treated patients with MAC-LD receive a nonstandard regimen: 20% are given macrolide monotherapy, and 33% of regimens are associated with emergent macrolide resistance.[37] The major risk factors for macrolide resistance include not only macrolide monotherapy but also macrolide plus a single drug (rifampicin, ethambutol, or fluoroquinolone).[31,38,39]

Similar to multidrug resistant tuberculosis, macrolide-resistant MAC-LD has a progressive disease course with limited therapeutic options.[34] As reported in one meta-analysis of 319 patients with macrolide-resistant MAC-LD, the sputum culture conversion rate after a combination of multiple antibiotics including fluoroquinolone and aminoglycoside or surgical resection was only 21%.[40] Notably, the treatment outcome was similar between patients with NB and fibrocavitary types. Although the

2017 BTS guideline recommends the use of isoniazid or moxifloxacin instead of macrolide in treatment for macrolide-resistant MAC-LD, the clinical efficacy of such a regimen remains uncertain.[2] Other potential treatment options include clofazimine, prolonged amikacin injection, amikacin liposomal inhalation suspension, and adjuvant surgery.[40]

Prognosis, treatment response, and recurrence

Generally, the long-term prognosis of patients with MAC-LD is poor, and a pooled estimate of the 5-year all-cause mortality rate is approximately 27%. Advanced age, male sex, and comorbidities were found to be risk factors of mortality in patients with MAC-LD.[41] A recently published systemic review investigated 2748 patients with MAC-LD enrolled in 42 studies and reported that in 52.3% cases with treatment using a macrolide-containing regimen, sputum conversion occurred without recurrence. Moreover, in treatment-naïve patients without macrolide resistance, the treatment success rate was 61.4% when three-drug therapy was employed and further increased to 65.7% when the treatment lasted >1 year.[42] To improve outcomes in patients with MAC-LD, physicians should actively adhere to guideline-based standard therapy.

However, even after treatment for MAC-LD has been completed, disease recurrence can occur, which is defined as two positive MAC cultures following culture conversion.[15] In a South Korean study involving 402 patients with MAC-LD, NTM-LD developed again after successful treatment in 118 (29%) patients, with MAC species accounting 55% of the recurrent cases (n = 65). For the 65 recurrent MAC-LD cases, genotyping revealed a 74% rate of reinfection with new MAC strains and a 26% rate of relapse of the original strain.[20] MAC-LD recurrence predominantly resulted from reinfection rather than relapse; thus, physicians should consider macrolide-based three-drug therapy for previously treated disease, because recurrence itself was not always correlated with macrolide resistance.[36]

Conclusion

The disease burden of MAC-LD is increasing, and MAC-LD treatment remains challenging. Physicians should consider antibiotic treatment for patients with severe MAC-LD (refractory symptoms or cavitary disease) and those with disease progression (clinical deterioration or radiographic progression). With adherence to macrolide-based three-drug therapy, treatment success can be expected in two thirds of patients without macrolide resistance. By contrast, only one fifth of macrolide-resistant patients have sputum culture conversion. To prevent macrolide resistance and improve treatment response, physicians should use standard three-drug therapy to treat MAC-LD rather than macrolide monotherapy or macrolide combined with a single drug. Nevertheless, because of long-term treatment course and unmet response, potential drugs should still be developed to treat patients with MAC-LD, a population that is estimated to grow in the future.

Author contributions

Pan SW, and Shu CC conceptualized this review. Pan SW, Shu CC, Feng JY and Su WJ were involved in manuscript preparation. Professors Su was responsible for coordination.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work is supported by Taiwan Society of Pulmonary and Critical Care Medicine and partially by Taipei Veterans General Hospital (Grant No. V109C-053).

References

1. Fedrizzi T, Meehan CJ, Grottola A, Giacobazzi E, Fregni Serpini G, Tagliazucchi S, et al. Genomic characterization of nontuberculous mycobacteria. *Sci Rep* 2017;**7**:45258.
2. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax* 2017;**72**(Suppl 2):ii1—64.
3. Park YS, Lee CH, Lee SM, Yang SC, Yoo CG, Kim YW, et al. Rapid increase of non-tuberculous mycobacterial lung diseases at a tertiary referral hospital in South Korea. *Int J Tubercul Lung Dis* 2010;**14**:1069—71.
4. Al Houqani M, Jamieson F, Chedore P, Mehta M, May K, Marras TK. Isolation prevalence of pulmonary nontuberculous mycobacteria in Ontario in 2007. *Canc Res J* 2011;**18**:19—24.
5. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med* 2012;**185**:881—6.
6. Chien JY, Lai CC, Sheng WH, Yu CJ, Hsueh PR. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000-2012. *Emerg Infect Dis* 2014;**20**:1382—5.
7. Huang HL, Cheng MH, Lu PL, Shu CC, Wang JY, Wang JT, et al. Epidemiology and predictors of NTM pulmonary infection in Taiwan-a retrospective, five-year multicenter study. *Sci Rep* 2017;**7**:16300.
8. Jang MA, Koh WJ, Huh HJ, Kim SY, Jeon K, Ki CS, et al. Distribution of nontuberculous mycobacteria by multigene sequence-based typing and clinical significance of isolated strains. *J Clin Microbiol* 2014;**52**:1207—12.
9. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med* 2015;**36**:13—34.
10. van Ingen J, Wagner D, Gallagher J, Morimoto K, Lange C, Haworth CS, et al. Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. *Eur Respir J* 2017;**49**:1601855.
11. Koh WJ, Jeong BH, Jeon K, Lee NY, Lee KS, Woo SY, et al. Clinical significance of the differentiation between Mycobacterium avium and Mycobacterium intracellulare in M avium complex lung disease. *Chest* 2012;**142**:1482—8.
12. Tortoli E, Rindi L, Garcia MJ, Chiaradonna P, Dei R, Garzelli C, et al. Proposal to elevate the genetic variant MAC-A, included in the Mycobacterium avium complex, to species rank as Mycobacterium chimaera sp. nov. *Int J Syst Evol Microbiol* 2004;**54**:1277—85.

13. Boyle DP, Zembower TR, Reddy S, Qi C. Comparison of clinical features, virulence, and relapse among Mycobacterium avium complex species. *Am J Respir Crit Care Med* 2015;**191**:1310—7.
14. Pan SW, Shu CC, Feng JY, Chien JY, Wang JY, Chan YJ, et al. Impact of different subspecies on disease progression in initially untreated patients with *Mycobacterium avium* complex lung disease. *Clin Microbiol Infect* 2020 April 19. https://doi.org/10.1016/j.cmi.2020.04.020. S1198-743X(20)30228-7, [published online ahead of print, 2020 Apr 28].
15. Hwang JA, Kim S, Jo KW, Shim TS. Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course. *Eur Respir J* 2017;**49**:1600537.
16. Ito Y, Hirai T, Maekawa K, Fujita K, Imai S, Tatsumi S, et al. Predictors of 5-year mortality in pulmonary Mycobacterium avium-intracellulare complex disease. *Int J Tubercul Lung Dis* 2012;**16**:408—14.
17. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, 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.
18. Tsukamura M. Diagnosis of disease caused by Mycobacterium avium complex. *Chest* 1991;**99**:667—9.
19. Huang HL, Lee MR, Liu CJ, Cheng MH, Lu PL, Wang JY, et al. Predictors of radiographic progression for NTM-pulmonary disease diagnosed by bronchoscopy. *Respir Med* 2019;**161**:105847.
20. Koh WJ, Moon SM, Kim SY, Woo MA, Kim S, Jhun BW, et al. Outcomes of Mycobacterium avium complex lung disease based on clinical phenotype. *Eur Respir J* 2017;**50**:1602503.
21. Lee G, Lee KS, Moon JW, Koh WJ, Jeong BH, Jeong YJ, et al. Nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc* 2013;**10**:299—306.
22. Kitada S, Uenami T, Yoshimura K, Tateishi Y, Miki K, Miki M, et al. Long-term radiographic outcome of nodular bronchiectatic Mycobacterium avium complex pulmonary disease. *Int J Tubercul Lung Dis* 2012;**16**:660—4.
23. Loebinger MR. Mycobacterium avium complex infection: phenotypes and outcomes. *Eur Respir J* 2017;**50**:1701380.
24. Pan SW, Shu CC, Feng JY, Wang JY, Chan YJ, Yu CJ, et al. Microbiological persistence in patients with Mycobacterium avium complex lung disease: the predictors and the impact on radiographic progression. *Clin Infect Dis* 2017;**65**:927—34.
25. Griffith DE. Treatment of Mycobacterium avium complex (MAC). *Semin Respir Crit Care Med* 2018;**39**:351—61.
26. Basavaraj A, Segal L, Samuels J, Feintuch J, Feintuch J, Alter K, et al. Effects of chest physical therapy in patients with non-tuberculous mycobacteria. *Int J Respir Pulm Med* 2017;**4**.
27. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017;**50**:1700629.
28. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. *Emerg Infect Dis* 2009;**15**:1556—61.
29. Jeong BH, Jeon K, Park HY, Kim SY, Lee KS, Huh HJ, et al. Intermittent antibiotic therapy for nodular bronchiectatic Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2015;**191**:96—103.
30. Kwon YS, Koh WJ, Daley CL. Treatment of Mycobacterium avium complex pulmonary disease. *Tuberc Respir Dis* 2019;**82**:15—26.
31. Griffith DE, Brown-Elliott BA, Langsjoen B, Zhang Y, Pan X, Girard W, et al. Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2006;**174**:928—34.
32. Brown-Elliott BA, Iakhiaeva E, Griffith DE, Woods GL, Stout JE, Wolfe CR, et al. In vitro activity of amikacin against isolates of Mycobacterium avium complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. *J Clin Microbiol* 2013;**51**:3389—94.
33. Daley CL. Mycobacterium avium complex disease. *Microbiol Spectr* 2017;**5**. https://doi.org/10.1128/microbiolspec.TNMI7-0045-2017.
34. Morimoto K, Namkoong H, Hasegawa N, Nakagawa T, Morino E, Shiraishi Y, et al. Macrolide-resistant Mycobacterium avium complex lung disease: analysis of 102 consecutive cases. *Ann Am Thorac Soc* 2016;**13**:1904—11.
35. Christianson S, Grierson W, Wolfe J, Sharma MK. Rapid molecular detection of macrolide resistance in the Mycobacterium avium complex: are we there yet? *J Clin Microbiol* 2013;**51**:2425—6.
36. Jhun BW, Kim SY, Moon SM, Jeon K, Kwon OJ, Huh HJ, et al. Development of macrolide resistance and reinfection in refractory Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2018;**198**:1322—30.
37. Brode SK, Chung H, Campitelli MA, Kwong JC, Marchand-Austin A, Winthrop KL, et al. Prescribing patterns for treatment of Mycobacterium avium complex and M. Xenopi pulmonary disease in ontario, Canada, 2001-2013. *Emerg Infect Dis* 2019;**25**. https://doi.org/10.3201/eid2507.181817.
38. Field SK, Fisher D, Cowie RL. Mycobacterium avium complex pulmonary disease in patients without hiv infection. *Chest* 2004;**126**:566—81.
39. Kim HJ, Lee JS, Kwak N, Cho J, Lee CH, Han SK, et al. Role of ethambutol and rifampicin in the treatment of Mycobacterium avium complex pulmonary disease. *BMC Pulm Med* 2019;**19**:212.
40. Park Y, Lee EH, Jung I, Park G, Kang YA. Clinical characteristics and treatment outcomes of patients with macrolide-resistant Mycobacterium avium complex pulmonary disease: a systematic review and meta-analysis. *Respir Res* 2019;**20**:286.
41. Diel R, Lipman M, Hoefsloot W. High mortality in patients with Mycobacterium avium complex lung disease: a systematic review. *BMC Infect Dis* 2018;**18**:206.
42. Diel R, Nienhaus A, Ringshausen FC, Richter E, Welte T, Rabe KF, et al. Microbiologic outcome of interventions against Mycobacterium avium complex pulmonary disease: a systematic review. *Chest* 2018;**153**:888—921.