

Nontuberculous Mycobacterial Lung Disease: Diagnosis and Treatment

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Nontuberculous mycobacteria (NTM) are ubiquitous organisms with a broad spectrum of virulence that are responsible for opportunistic infections. Chronic lung infection, the most common complication, affects 94% of individuals infected with NTM¹. Most common chronic lung infection related with NTM *Mycobacterium avium* complex (MAC) and this pathogen is responsible for 80% to 86% of lung infections, and M abscesses is associated with 6% to 13%²⁻⁴.

While NTM exposure is nearly universal, NTM disease is relatively rare. Thus, it is increasingly accepted that infection requires not only exposure to NTM but also some type of predisposition NTM lung disease occurs primarily in 2 groups of patients:

- Those with anatomic lung abnormalities that typically do not have a readily identified genetic basis (e.g. bronchiectasis, chronic obstructive pulmonary disease or pneumoconiosis, particularly silicosis)
- Those with immunologic or genetic disorders that predispose to bronchiectasis and or lung infections (e.g. cystic Fibrosis, primary ciliary dyskinesia, or alpha-1-antitrypsin deficiency)

However, some patients with NTM lung disease have no overt lung or immunologic abnormalities. It is increasingly clear that bronchiectasis and NTM lung disease are closely related disorders⁵. A meta-analysis showed that the overall prevalence of NTM infection was 9,3,4 in patients with bronchiectasis⁶.

An additional risk factor for NTM disease is the use of tumor necrosis factor- α (TNF- α) blockers, which can be associated with severe, potentially fatal NTM lung disease^{4,7} and thus, patients should be evaluated for NTM disease before anti-TNF- α therapy is instituted, and these agents must be used with extreme caution in patients with established NTM disease⁸. There is also growing concern about corticosteroid use in NTM disease⁹.

There are two major patterns of NTM lung disease: the fibrocavitary and nodular bronchiectatic subtypes. The fibrocavity form of NTM lung disease has historically been described as affecting older men with underlying chronic obstructive pulmonary disease (COPD) and a history of smoking. It is characterized radiographically by cavities with areas of increased opacity, usually in the upper lobes¹⁰. Pleural thickening and volume loss by fibrosis with traction bronchiectasis are frequently observed. Unlike pulmonary tuberculosis, NTM lung disease tends to cause thin-walled cavities, often involving pleura without lymph node calcification, and no atelectasis¹¹.

The nodular bronchiectasis of NTM lung disease is characterized by bilateral, multilobar bronchiectasis, especially in the middle and lower lung fields, with small nodules on chest radiography and high-resolution computed tomography¹². This subtype, sometimes called Lady Windermere Syndrome, occurs predominantly in older nonsmoking women who don't have underlying lung disease. Other common associated features are low body mass index, white race, pectus excavatum, scoliosis, and mitral valve prolapse^{6,13}.

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) have joint guidelines for management of NTM diseases¹⁴. For diagnosis, the guidelines require a triad symptoms, radiographic findings, and microbiologic results.

The most common symptoms of NTM lung disease are persistent cough, fatigue, weight loss, night sweats, dyspnea, fever (for those with disseminated infection), and hemoptysis. Conditions that can present similarly to NTM lung disease are recurrent aspiration pneumonitis, bronchiectasis, TB, lung cancer, aspergillosis, and fungal diseases such as blastomycosis, histoplasmosis, and coccidiomycosis.

Typical radiographic findings with NTM lung disease are:

- Reticulonodular infiltrates
- Multiple nodules
- Multifocal bronchiectasis
- Nodules and bronchiectasis occurring in the same lobe, often the right middle lobe lingual.
- Cavities
- Alveolar infiltrates

A plain chest radiograph may be adequate for evaluating patients with fibrocavitary disease, RCT of the chest is now routinely indicated to demonstrate the characteristic abnormalities or nodular bronchiectatic NTM lung disease^{11,15}. Because NTM are ubiquitous, a single positive pulmonary specimen does not fulfill microbiologic criteria for infection. The guidelines require 1 of the following¹⁶.

- Positive culture results from at least 2 separate expectorated sputum samples; if the results are nondiagnostic, consider repeat sputum AFB smears and cultures. For patients unable to produce sputum, sputum can also be induced.

- Positive culture result at least 1 bronchial wash or lavage

Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or

- Biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and 1 or more sputum or bronchial washings that are culture-positive for NTM

Patients who have characteristic symptoms and imaging findings of NTM lung disease, but do not meet the microbiological criteria, should be followed with intermittent collection of sputum and close monitoring of symptoms until the diagnosis is firmly established or excluded¹⁷.

No drugs have been approved by the US Food and Drug Administration (FDA) for treatment of NTM lung disease. Because the disease is a relatively rare, there have been no randomized trials; the evidence base is largely composed of single-center observational studies. The current treatment regimens are species-specific¹⁸. For unknown reasons, the chance of success in treating MAC lung disease diminishes with each treatment effort, even with maintenance of in vitro macrolide susceptibility¹⁹. Therefore, drug susceptibility testing should be performed before initial MAC therapy; The first attempt at MAC therapy should be as aggressive as possible, and adequate regimen should be maintained to prevent the emergence of macrolide-resistant

strains²⁰. For patients with MAC with extensive disease, at least 2 months of intermittent (twice or thrice weekly) streptomycin or amikacin is recommended, although longer parenteral therapy may be desirable in patents with very extensive disease or for those who do not tolerate other agents.

There is no established treatment regimen for M abscessus spp. abscessus. Considering drug toxicity and inconvenience, some centers²¹. Recommend an initial intensive phase of daily clarithromycin or azithromycin and 2 parenteral drugs for 2 to 4 months, followed by macrolide therapy with at least 1 other oral agent or inhaled amikacin as step-down therapy. If the isolate is identified as M abscessus spp. meassiliense or M abscessus spp. bollet; the macrolide should not be used, and inhaled amikacin plus clofazimine should be considered in the continuation phase. Recent studies on the use of clofazimine in a multi-drug regimen demonstrate tolerability and efficacy in MAC and the M abscessus complex.

Type of disease	Regimen
Nodular/ bronchiectatic disease	1. Chlar/dayithromycin 1000 mg tiw or azithromycin 500 to 600 mg 2. Ethambutol 25 mg/kg tiw 3. Rifampin 600 mg tiw
Cavitary Disease	1. Clarithromycin 500 to 1000 mg/day or azithromycin 250 to 300 mg/day 2. Ethambutol 15 mg/kg daily 3. Rifampin 450 to 600 mg/daily 4. Consider streptomycin or amikacin 15 mg/kg tiw for first 2 to 3 months
Advanced or previously treated disease	1. Clarithromycin 500 to 1000 mg/day or azithromycin 250 to 300 mg/day and 2. Ethambutol 15 mg/kg daily 3. Rifabutin 150 to 300 mg/daily or Rifampin 450 to 600 mg/daily 4. Include streptomycin or amikacin 15 mg/kg tiw for first 2 to 3 months
Tiw, three times per week. Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al.: An official ATS/IDSA statement: Diagnosis; treatment; and prevention of nontuberculosis mycobacterial disease. Am J Respir. Crit. Care Med. 175: 367-416,2007	

Table 1: Treatment of Pulmonary Disease due to Mycobacterium avium Complex Infections

Macrolide-resistant MAC lung disease is associated with a poor prognosis²².

The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or macrolide treatment with inadequate companion medications. The treatment strategy associated with highest rates of success for macrolide-resistant MAC lung disease includes the use of anti-drug regimen; including a parenteral aminoglycoside and surgical resection (“debulking”) of diseased lung²³. The optimal drug regimen for treating macrolide-resistant strains is unknown but some experts recommend ethambutol, rifabutin, an injectable agent, and possibly another oral drug such as an 8-methoxyl flouroquinolone or clofazimine²³.

Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery should be considered for surgery under the following conditions: (1) poor response

to the drug therapy, (2) development of macrolide-resistant MAC disease, or (3) presence of significant disease-related complications, such as hemoptysis. Patients are typically treated with intensive antibiotic regimens for 2 to 3 months prior to surgery, to maximally reduce bacterial burden⁷.

Lung resectional surgery for mycobacterial disease is potentially associated with significant morbidity and mortality, so it should be performed by a thoracic surgeon who has considerable experience with mycobacterial disease. Eligible patients should be referred to a surgical center as early as possible in their treatment course.

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