

NTM Pulmonary Disease

The Disease is worse Than the Treatment

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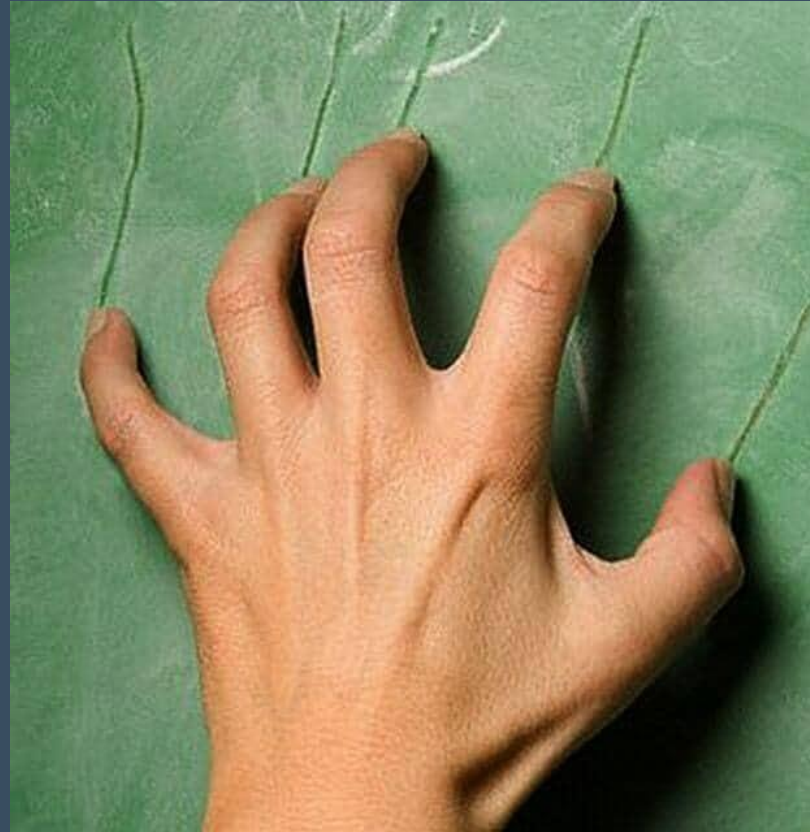
Cleveland Clinic Foundation



Learning Objectives

- Upon completion of this learning activity, participants should be able to:
 - Identify NTM pulmonary disease
 - Explain the risks of under-treating NTM pulmonary disease
 - Recognize the efficacy and safety of appropriate pharmacologic therapy

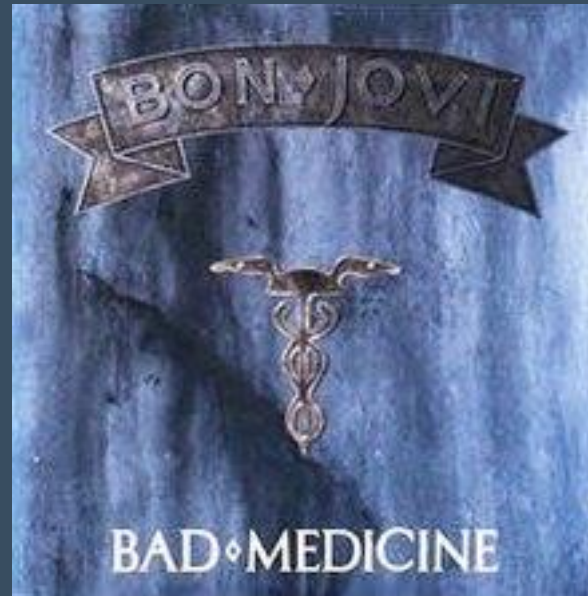
Treatment is Worse than the Disease



<https://scienceblog.com/48773/its-anatomys-fault-why-fingernails-on-chalkboards-irritate/>



The Disease



“There ain’t no doctor that can cure my disease...”

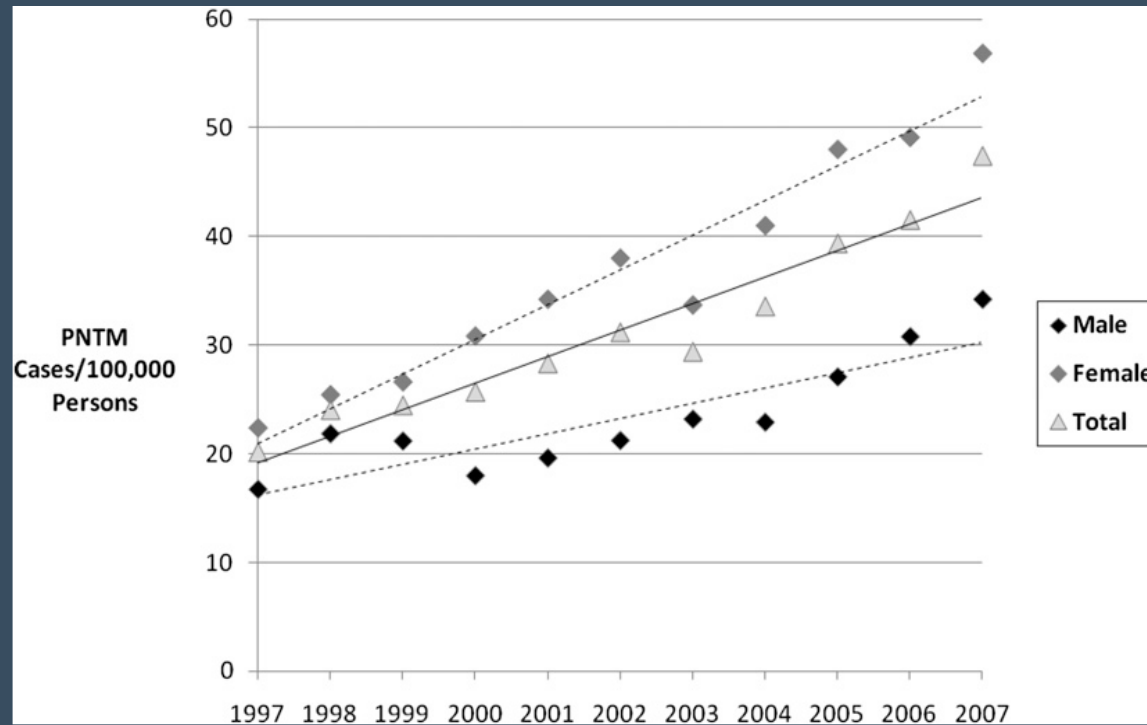
Nontuberculous Mycobacteria (NTM)

- All mycobacteria except for TB and leprosy
- Found everywhere → water and soil
- Form biofilms on surfaces they occupy
- Most disease in humans is pulmonary
 - Prevalence increasing nearly 8% per year

Prevalence of Nontuberculous Mycobacterial Lung Disease in U.S. Medicare Beneficiaries

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NTM Pulmonary Disease

- About 200 species of NTM
- Nearly 80% of NTM pulmonary disease in the US is caused by Mycobacterium Avium Complex (MAC)
 - MAC the most studied with clearest diagnostic criteria and treatment regimens

MAC Pulmonary Disease

- MAC subspecies include:
 - a. *M. avium*
 - b. *M. intracellulare*
 - c. *M. chimaera*
 - d. *M. vulneris*
 - e. *M. colombiense*
 - f. *M. mantenii*
 - g. *M. arosiense*
 - h. *M. timonense*
 - i. *M. bouchedurhonense*
 - j. *M. marseillense*
 - k. *M. paraintracellulare*
 - l. *M. yongonense*



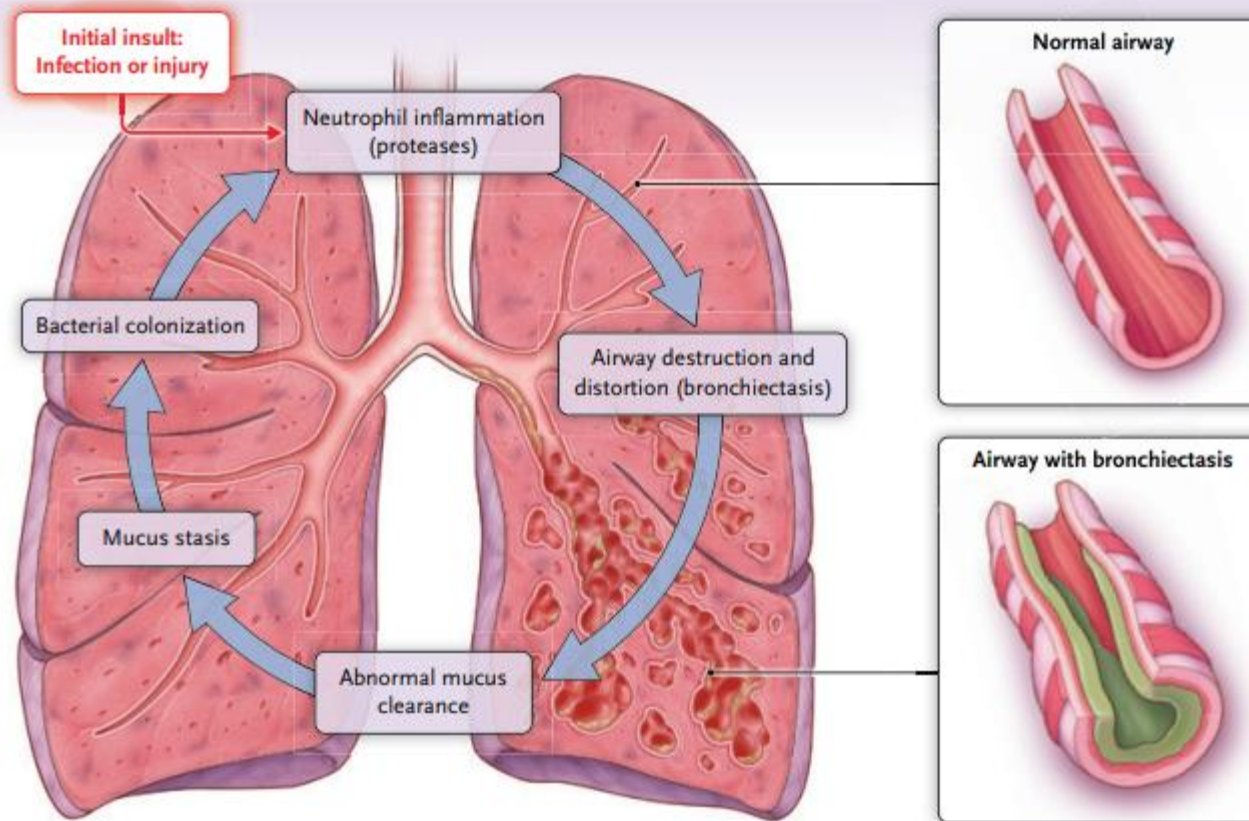
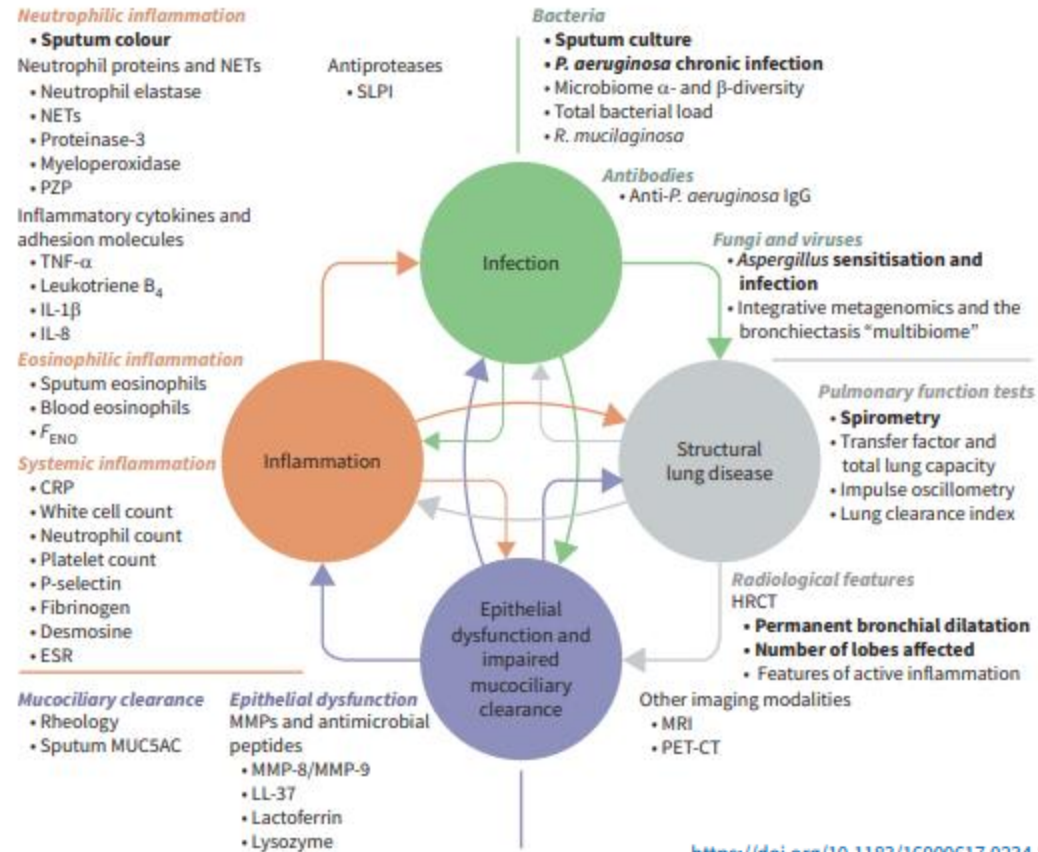


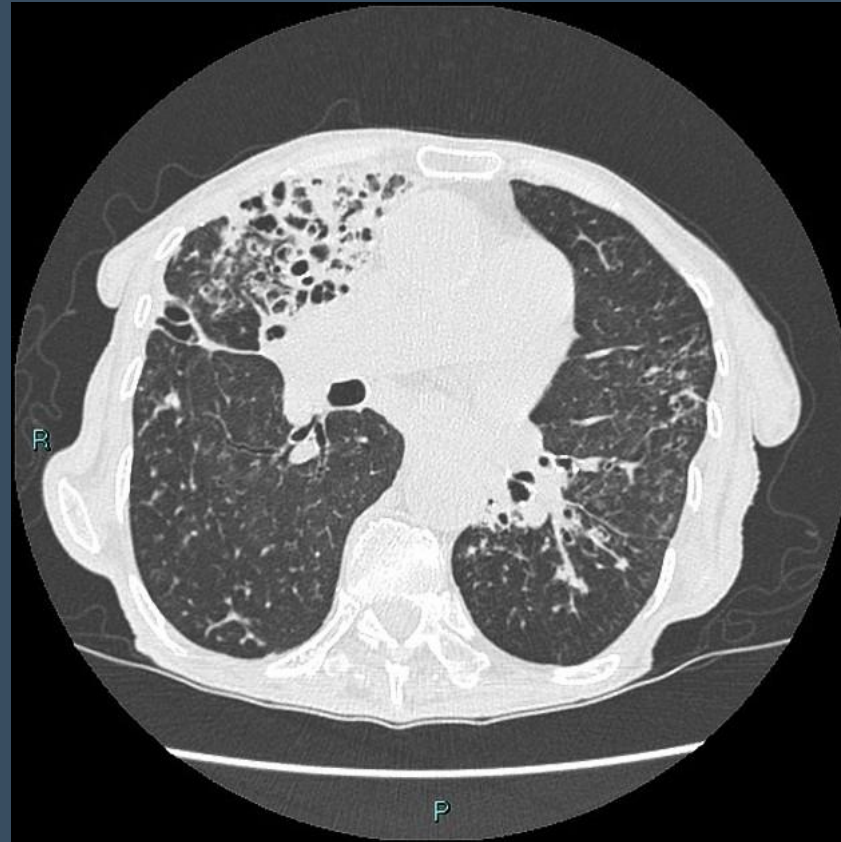
Figure 1. Pathobiologic Mechanisms of Bronchiectasis.

Shown is Cole's "vicious cycle" of infection, inflammation, mucus stasis, and tissue damage in the pathogenesis of bronchiectasis.²² The insets show a normal airway and one with the impaction of mucus that is central to the pathobiologic features of bronchiectasis.

Vicious Vortex



NTM



<https://radiopaedia.org/cases/pulmonary-mycobacterium-avium-complex-infection-1>

Risk Factors for NTM Pulmonary Disease

- Chronic lung disease
 - **Bronchiectasis**, asthma, COPD, etc.
- Low body weight and thoracic skeletal abnormalities
- Immunosuppression
 - Including inhaled corticosteroids



Diagnostic Criteria

- **ATS/IDSA Criteria**
 - Clinical – need symptoms (non-respiratory ones count too!)
 - Radiographic – compatible CT changes
 - Microbiologic – at least 2 separate expectorated sputum cultures growing the same NTM or 1 bronchoscopic culture

NTM Pulmonary Disease

- Most common symptoms reported
 - Fatigue 77%
 - Productive cough 71%
 - Dyspnea 66%
 - Dry cough 51%
 - Night Sweats 49%
 - Weight loss 43%
 - Hemoptysis 34%
 - Loss of appetite 33%
 - Chest pain 31%
 - Anxiety 31%

NTM Pulmonary Disease

- Physicians under-estimate morbidity and mortality of NTM lung disease
- Often delayed diagnosis
 - Low index of suspicion
 - Nonspecific symptoms
 - Symptoms overlap with their underlying lung disease
 - CXR can be normal in early disease

Risk Factors for Progression of NTM Pulmonary Disease

- Smear positive
- Cavitory disease
- BMI < 20
- Immunosuppression
 - Including inhaled corticosteroids





<https://en.wikipedia.org/wiki/Tornado>



NTM Pulmonary Disease

- 57% of patients had symptoms for > 1 year at time of diagnosis
- Delayed diagnosis → progressive decline in lung function and irreversible airway destruction
 - Lower FVC and FEV1 with higher disease severity and those with treatment failure

Kotilainen H *et al.* Eur J Clin Microbiol Infect Dis. 2015;34(9):1909-1918.

O'Connell ML *et al.* Chest. 2012;141(5):1203-1209.

Park HJ *et al.* Int J Tuberc Lung dis. 2023;27(6):465-470.

Park HY *et al.* Chest 2016;150(6):1222-1232.



<https://en.wikipedia.org/wiki/Tornado>



BMJ Open Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease

Mina Gochi,¹ Noboru Takayanagi,¹ Tetsu Kanauchi,² Takashi Ishiguro,¹ Tsutomu Yanagisawa,¹ Yutaka Sugita¹

To cite: Gochi M, Takayanagi N, Kanauchi T, et al. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease. *BMJ Open* 2015;5:e008058. doi:10.1136/bmjopen-2015-008058

ABSTRACT

Objectives: Some patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease (NB MAC-LD) deteriorate and die. The main aim of the study is to evaluate the prognostic factors and radiographic outcomes in patients with NB MAC-LD.

Setting: Retrospective single-centre review.

Participants: 782 HIV-negative patients with NB MAC-LD treated at our institution in Japan.

Primary and secondary outcome measures:

Strengths and limitations of this study

The present study clarified the prognostic factors for all-cause mortality and for radiographic deterioration of patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease (NB MAC-LD). Since treatment decisions were made by individual physicians, we could not assess which patients should be treated or which patients should undergo evaluation only.

■ Ten-year mortality rates from all causes and

41% of patients with nodular bronchiectatic MAC pulmonary disease experienced radiographic worsening over a follow up period of 5 years, more than half with worsening by 10 years

- **Vast majority were not treated (or suboptimal)**




CrossMark

Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course

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 @ERSpublications

Host predisposing factors are relatively more important than microbiological factors in stable MAC-LD patients <http://ow.ly/nf9N306AQd0>

Cite this article as: Hwang JA, Kim S, Jo K-W, *et al.* Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course. *Eur Respir J* 2017; 49: 1600537 [<https://doi.org/10.1183/13993003.00537-2016>].

- 62% of MAC-LD patients progressed radiographically within 3 years, leading to initiation of antibiotic treatment
- 23% with radiographic stability

Health Care Utilization

- NTM lung disease in the first year of follow up:
 - 5x increased risk of hospitalization
 - 155% higher health care expenditures

NTM Pulmonary Disease

- Common thinking:
 - Rarely needs to be treated
 - Treatment makes you feel worse than the disease
 - Not that serious
 - No follow-up needed, call if symptoms



Treatment is Worse than the Disease



Disease Worse Than Treatment

Diel et al. *BMC Infectious Diseases* (2018) 18:206
<https://doi.org/10.1186/s12879-018-3113-x>

BMC Infectious Diseases

RESEARCH ARTICLE

Open Access



High mortality in patients with *Mycobacterium avium* complex lung disease: a systematic review

Roland Diel^{1,2}, Marc Lipman³ and Wouter Hoefsloot^{4*}

Abstract

Background: The incidence of nontuberculous mycobacterial (NTM) pulmonary disease caused by *Mycobacterium avium* complex (MAC) in apparently immune-competent people is increasing worldwide. We performed a systematic review of the published literature on five-year all-cause mortality in patients with MAC lung disease, and pooled the mortality rates to give an overall estimate of five-year mortality from these studies.

Methods: We systematically reviewed the literature up to 1st August 2017 using PubMed® and ProQuest Dialog™ to search Medline® and Embase® databases, respectively. Eligible studies contained > 10 patients with MAC, and numerical five-year mortality data or a treatment evaluation for this patient group. Mortality data were extracted and analysed to determine a pooled estimate of all-cause mortality.

Results: Fourteen of 1035 identified studies, comprising 17 data sets with data from a total of 9035 patients, were eligible. The pooled estimate of five-year all-cause mortality was 27% (95% CI 21.3–37.8%). A high degree of heterogeneity was observed ($I^2 = 96\%$). The mortality in the data sets varied between 10 and 48%. Studies predominantly including patients with cavitary disease or greater comorbidity reported a higher risk of death. Patients in Asian studies tended to have a lower mortality risk. Predictors of mortality consistent across studies included male sex, presence of comorbidities and advanced patient age.

Conclusions: Despite high heterogeneity, most studies in patients with MAC pulmonary disease document a five-year all-cause mortality exceeding 25%, indicating poor prognosis. These findings emphasise the need for more effective management and additional prospective mortality data collection.

Keywords: Infectious disease, Nontuberculous mycobacteria, NTM, Survival outcome

NTM Pulmonary Disease

- Reality:
 - 5 year all cause mortality ~ 25%
 - Up to 60% progress with watchful waiting.
 - The later you treat, the harder to cure
 - →AFB Smear (+), cavitory disease, BMI < 20
 - Most people tolerate guideline-based therapy
 - Azithromycin/ethambutol/rifampin for 12 months after the first negative sputum culture

First Line Treatment for NTM...



Airway Clearance

- Reduced need for antibiotics and symptoms
- More culture conversion
 - think “source control”
- Exercise
 - 150 min moderate intensity exercise per week (treadmill, stationary bike, yoga, core strength)
 - Pulmonary rehab
- Bronchodilators and Hypertonic saline
- Positive expiratory pressure devices
- Vest, Chest PT

The Treatment



“Gonna take more than a shot to get this poison out of me...”

The (Guideline Based) Treatment

- 12 months following culture conversion:
 - Azithromycin (or clarithromycin)
 - Ethambutol
 - Rifampin (or rifabutin)
- IV Amikacin (diffuse or cavitary disease)
- Inhaled liposomal amikacin (refractory disease)



The (Guideline Based) Treatment

- Side effects:
 - **Azithromycin** — GI common. QTc and hearing rare.
 - **Ethambutol** — well tolerated. Peripheral and optic neuropathy rare.
 - **Rifampin** — orange coloration of body fluids, GI common. Rare cytopenias, hepatitis, flu-like



Cure Rates on Treatment

- Culture conversion after starting GBT:
 - 83% and 94% within 6 months
 - 80% within 3 months
- Most patients were able to tolerate and complete therapy

Moon SM, Jhun BW, Daley CL, Koh WJ. Unresolved issues in treatment outcome definitions for nontuberculous mycobacterial pulmonary disease. *Letter. Eur Respir J.* 2019;53(5).

Griffith DE, Adjemian J, Brown-Elliott BA, et al. Semiquantitative culture analysis during therapy for *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med.* 2015;192(6):754-760.

Furuuchi K, Morimoto K, Kurashima A, et al. Treatment duration and disease recurrence following the successful treatment of patients with *Mycobacterium avium* complex lung disease. *Letter. Chest.* 2020. doi:10.1016/j.chest.2019.12.016.

ORIGINAL RESEARCH

Lack of Adherence to Evidence-based Treatment Guidelines for Nontuberculous Mycobacterial Lung Disease

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- When decision to treat, most are not treated appropriately
 - 13% (77/579) of regimens met ATS/IDSA guidelines
 - 87% (502/579) did not
 - 30% (174/579) had harmful regimens that increased the odds of macrolide resistance

Evaluation of *Mycobacterium Avium* Complex Pulmonary Disease Treatment Completion and Adherence to ATS/IDSA Guidelines

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- 2006-2014
- Half of new MAC treatment patients prescribed a non-guideline regimen
- Many regimens that increased macrolide resistance

Summary

- Untreated NTM lung disease will cause irreversible lung damage in many
- It is easy to scare patients away from treatment
- Most patients should be offered treatment
- Most patients tolerate pharmacologic guideline-based therapy

Summary

- Successful early treatment may forever alter the course of a patient's life
- For many, the disease is worse than the treatment...
- “It'll take more than a doctor to prescribe a remedy...”
(RT, RN, pharmD, microbiologists, dietician, optho, audiologists...)

Questions?

I'm happy to sidestep any questions you may have.



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