Can You Identify Patients with NTM?

Diagnosis, Treatment Selection, and Monitoring of Nontuberculous Mycobacterial Lung Disease

National Jewish Health®
Breathing Science is Life.®

This educational activity is provided by National Jewish Health and supported by an educational grant from Insmed.

National Jewish Health®

Accreditation

Accreditation Statement

National Jewish Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

National Jewish Health designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

National Jewish Health®

Disclosures

Faculty

- **David Griffith, MD** discloses that he is a consultant AN2 Therapeutics, Insmed and Spero Pharmaceuticals.
- **Shannon Kasperbauer, MD** discloses that she is on an advisory board for AN2 Therapeutics and Insmed as well as a speaker for NTMir and Paratek.

Faculty, Planners and Reviewers:

- **Charles Daley, MD** discloses that he is an investigator for Insmed and Spero and a consultant for Meiji. He is on an advisory board for Insmed, Johnson and Johnson, Spero, Paratek, Cipla, and Matinas and on a data management committee for Otsuka.
- Tilman Koelsch, MD, Robert Belknap, MD, Andrea Harshman, MHA, CHCP, CMP-HC, Meghan Brenner, MA and Mandy Comeau have no relevant financial relationships to report.

All relevant financial relationships among individuals in a position to control the content of this activity have been identified and mitigated according to the Standards of Integrity and Independence in Accredited Education.

National Jewish Health®

Faculty Introductions

Presenting Faculty:

David E. Griffith, MD
Professor of Medicine
Division of Mycobacterial and Respiratory Infections
National Jewish Health
University of Colorado Denver
Denver, Colorado

Shannon H. Kasperbauer, MD
Associate Professor of Medicine
Division of Mycobacterial and Respiratory Infections
National Jewish Health
University of Colorado Denver
Denver, Colorado

Contributing Faculty:

Tilman L. Koelsch, MD
Assistant Professor
Department of Radiology
National Jewish Health
Denver, Colorado

National Jewish Health®

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Apply best practices to the diagnosis of NTM-LD.
- Implement treatment based on the updated NTM guidelines and individual patient response and considerations.
- Incorporate data on current and emerging therapies into treatment strategies for NTM-LD.

National Jewish Health®

Chapter 1

Epidemiology and Overview

National Jewish Health®

Can You Identify Patients with NTM?

Diagnosis, Treatment Selection, and Monitoring of Nontuberculous Mycobacterial Lung Disease

I was previously healthy and now I develop bronchitis 3-4 times each year…

I feel like I am moving through molasses all day.

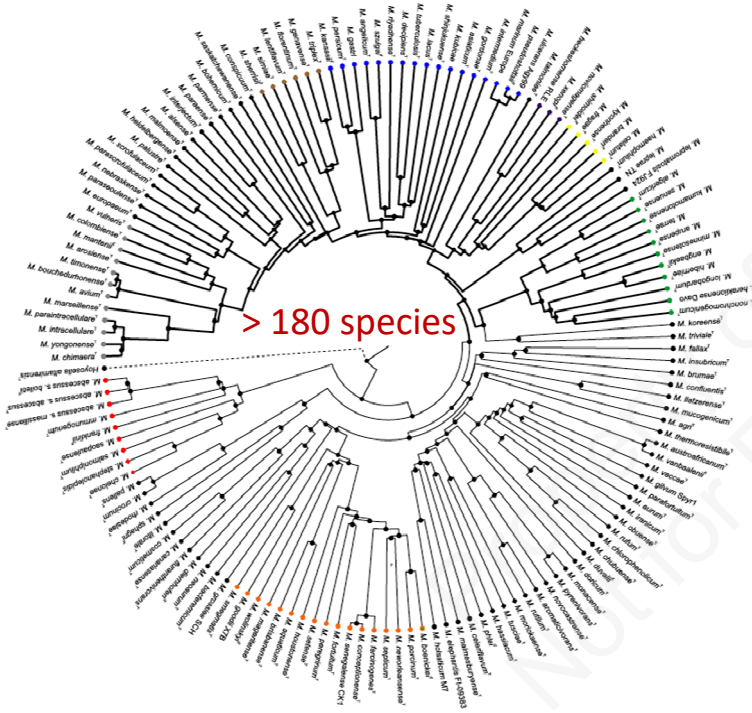
I stopped going to church because people were afraid to be around me with my productive cough.

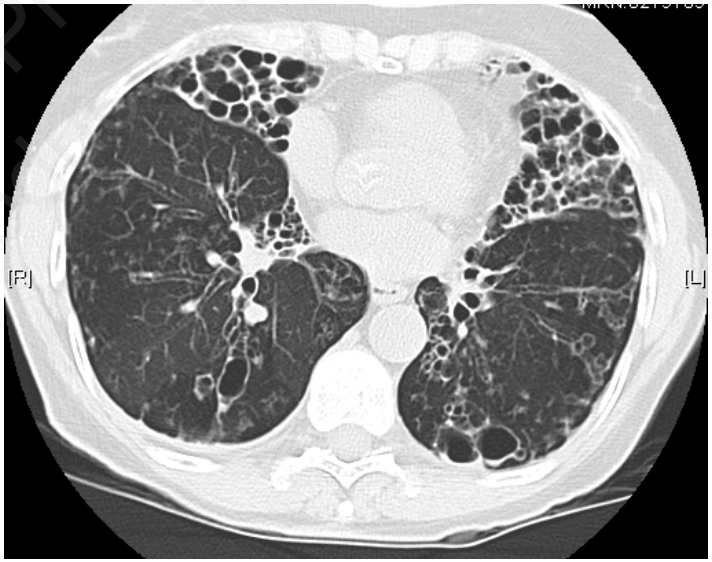
I am a runner, but it is getting harder for me to stay at my regular pace

The scariest time was waking up coughing up blood.

Can You Identify Patients with NTM?

Diagnosis, Treatment Selection, and Monitoring of Nontuberculous Mycobacterial Lung Disease





National Jewish Health®

Tortoli E et al. *Infect Genet Evol*. 2017 Dec;56:19-25

As Tuberculosis declines, NTM rates increase

22 studies reporting trends in rates of NTM disease

- Systematic review of studies reporting NTM rates between 1946 and 2014
- 22 studies reporting trends in rates of NTM disease (16 geographic areas over four continents)
- 75% of areas had climbing incidence rates
- Most studies (81%) showed declining TB incidence rates
- The proportion of incident mycobacterial disease caused by NTM was shown to be rising in almost every geographic area (94%)

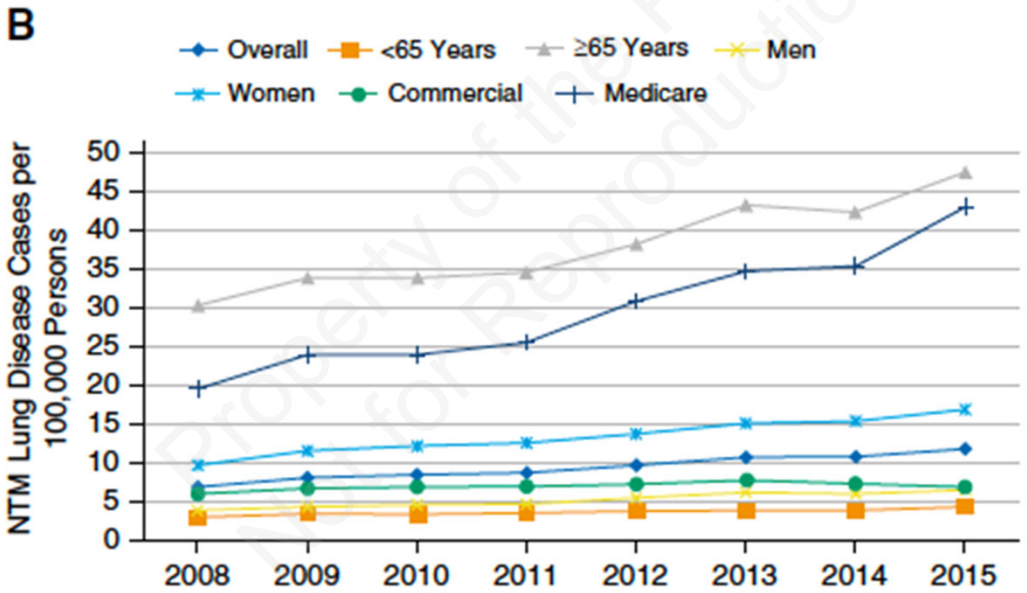
National Jewish Health®

Brode S et al. *Int J Tuberc Lung Dis*. 2014 Nov;18(11):1370-7.

Older individuals are at greater risk

National Managed Care Claims Database –
27 million people annually

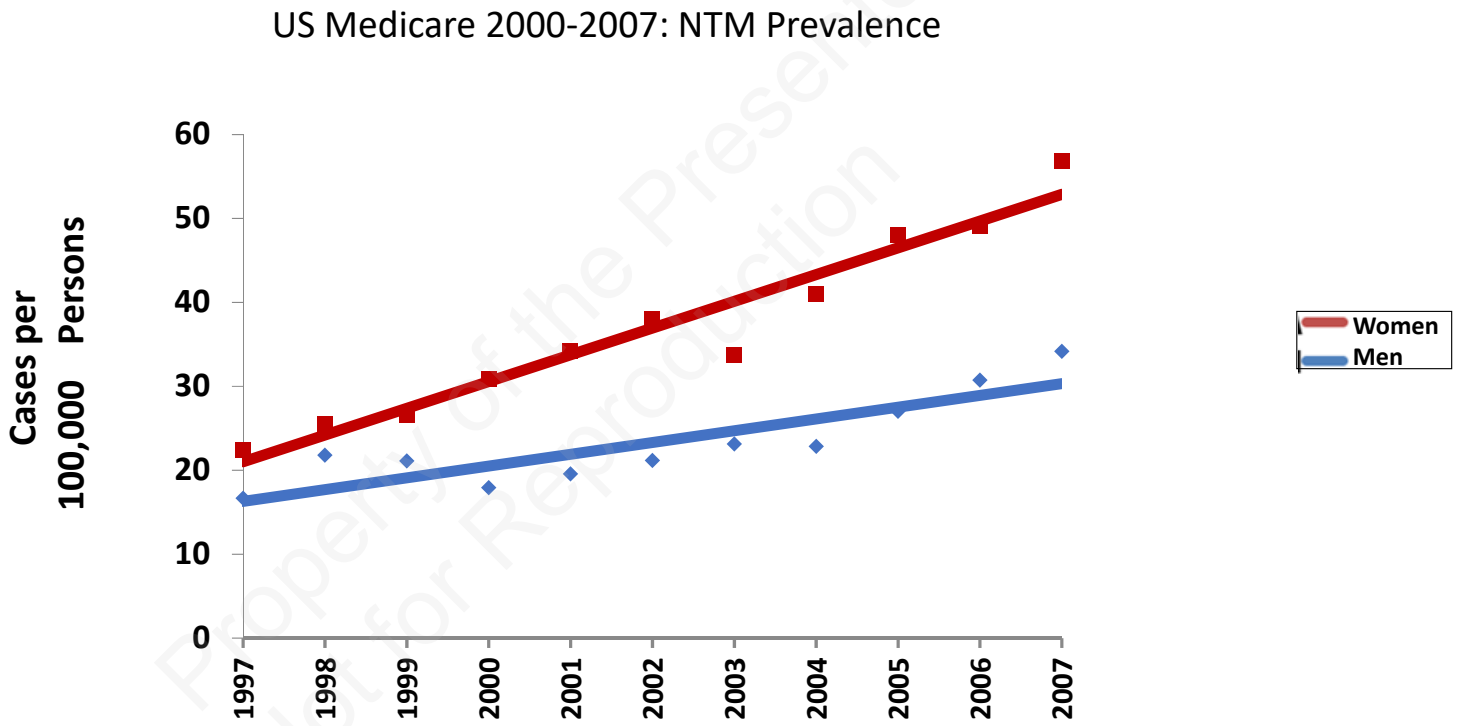
Prevalence (per 100,000)



Winthrop K et al. *Ann Am Thorac Soc*. 2020;17(2):178-185.

National Jewish Health®

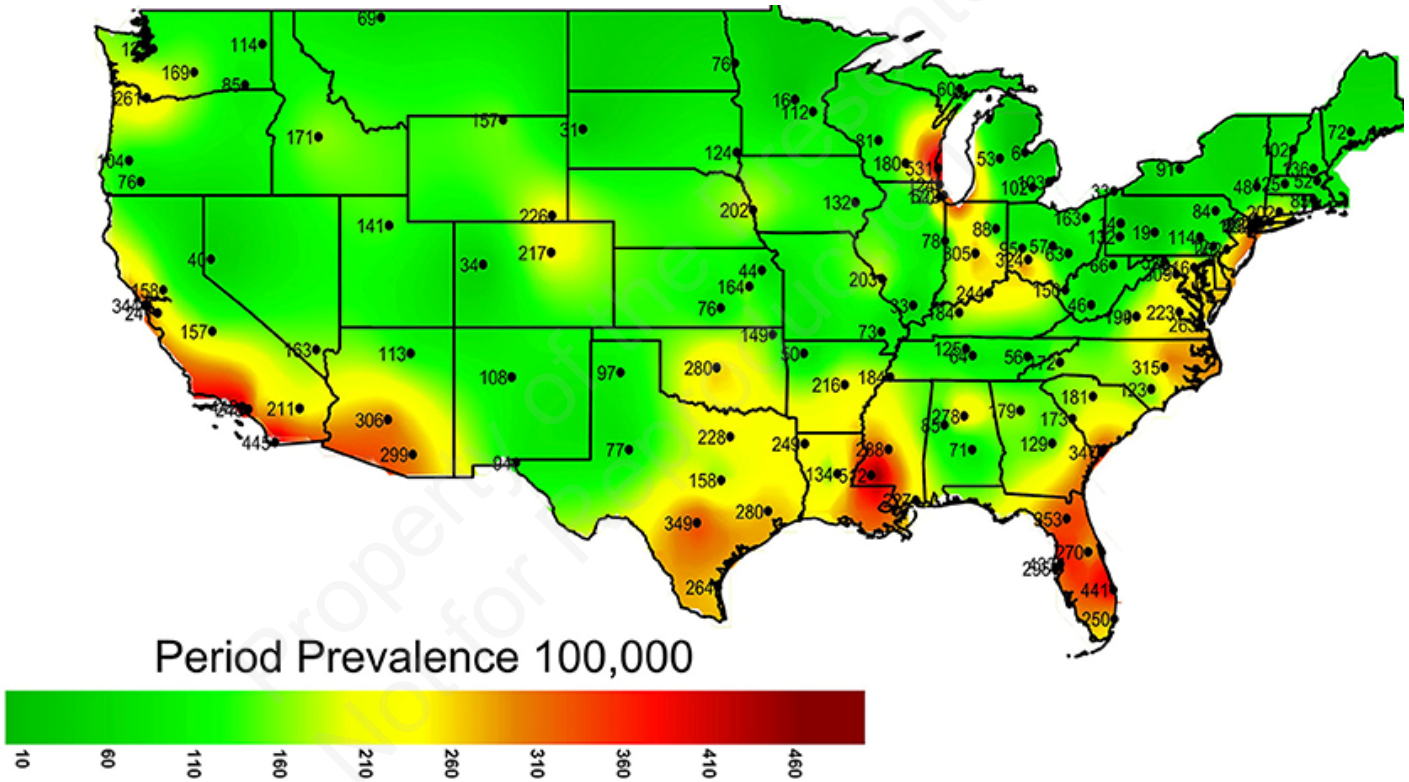
Women are affected more than men



National Jewish Health®

Adapted from Adjemian J et al. *Am J Respir Crit Care Med*. 2012;185(8):881–886.

Coastal regions see higher prevalence



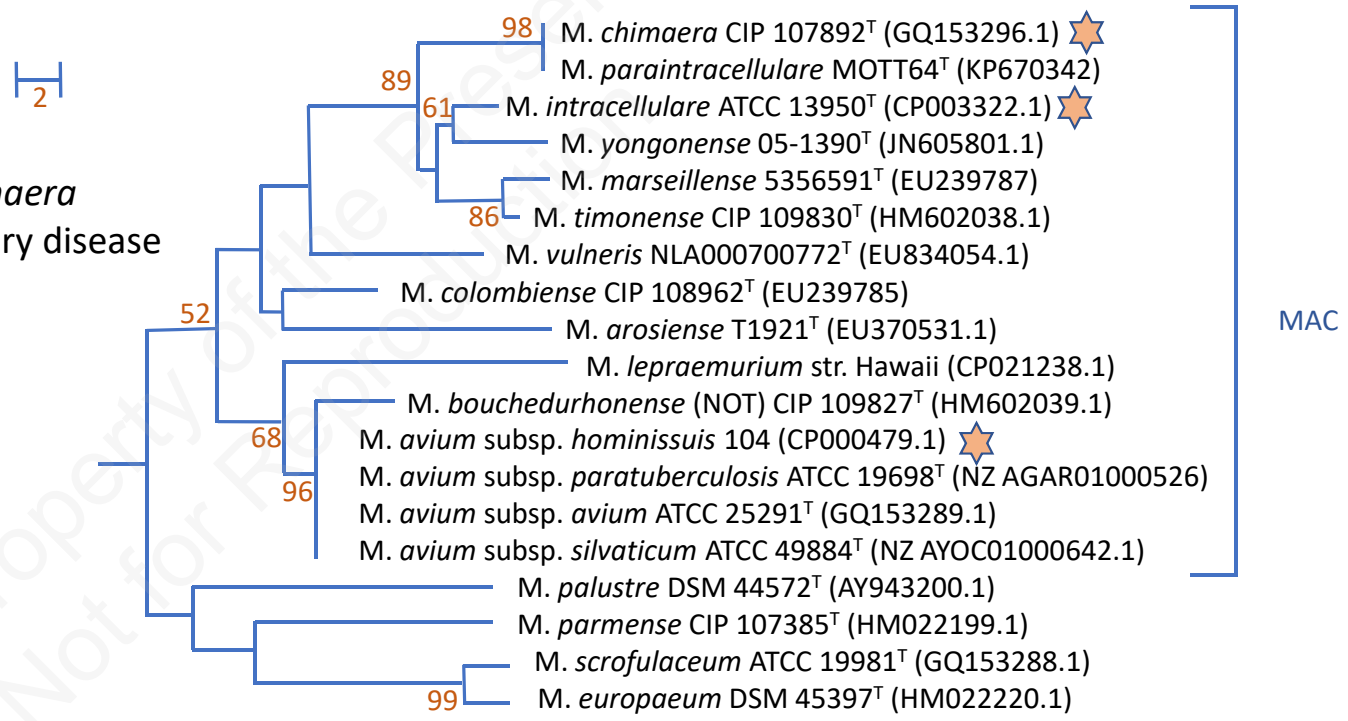
Pyarali FF et al. *Front Med* (Lausanne). 2018 Nov 6;5:311.

National Jewish Health®

Mycobacterium avium complex is the most common NTM pathogen

12 species of MAC

M. avium, *M. intracellulare*, and *M. chimaera* are the most common to cause pulmonary disease



National Jewish Health®

Adapted from International journal of systematic and evolutionary microbiology. , 2018, Vol.68(11), p.3666-3677.

Risk factors for NTM lung disease

NTM-LD OR was

- 7.6 for patients with **COPD** with no ICS use
- 19.6 for those who had ever used ICSs
- 29.1 for those with current ICS use.

  Andrejak C et al. *Thorax* 2013; 68(3): 256-262

Medicare recipients have high rates of NTM LD, 112 patients in 100,000

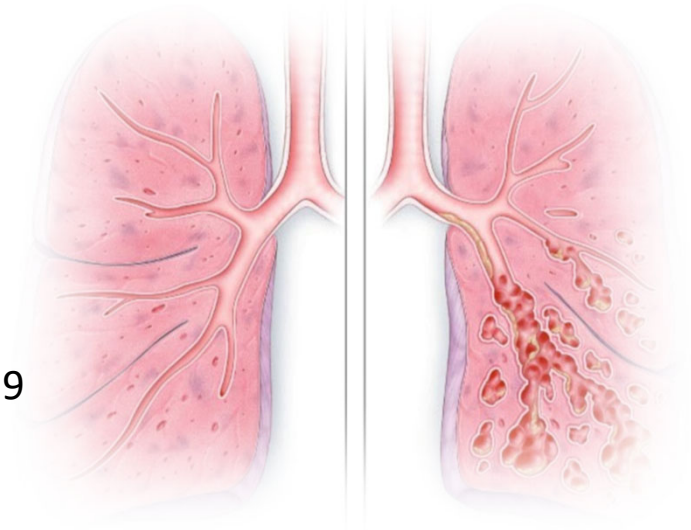
Adjemian J et al. *Am J Respir Crit Care Med* 2012; 185: 881–6.

The average prevalence rate for NTM infection in **veterans with COPD**, 148.9 patients in 100,000

Pyarali FF et al. *Front Med* (Lausanne). 2018 Nov 6; 5: 311.

In patients with **cystic fibrosis (CF)** the rate of NTM isolation is 12%

Salsgiver EL et al. *Chest* 2016;149 (2):390-400.



National Jewish Health®

N Engl J Med 2002; 346:1383-1393.

Epidemiology Summary

- NTM include approximately 200 species of mycobacteria that are found throughout our environment (soil and water)
- Members of *Mycobacterium avium* complex are the most common to cause pulmonary disease following by *M. abscessus*, *M. kansasii*, and *M. xenopi*
- There are 12 species of MAC of which *M. avium*, *M. intracellulare*, and *M. chimaera* are the most common to cause pulmonary disease
- NTM, including MAC, are increasing in prevalence in many areas of the world
- We recognize several risk factors for the development of NTM-LD, with bronchiectasis being a common denominator

National Jewish Health®

Chapter 2

Diagnosis of NTM

National Jewish Health®

Diagnosis of NTM Lung Disease: Clinical Suspicion

- Symptoms:
  - Cough, Sputum Production, Fatigue, Weight Loss, Hemoptysis
- Typical Morphotype:
  - Nodular/Bronchiectatic Disease: Thin, tall, post-menopausal female
  - Cavitary NTM Disease: Middle aged or older male, thin, with history of smoking, COPD

Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
Cowman S et al. Eur Respir J. 2019 Jul 11;54.
Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

National Jewish Health®

Diagnosis of NTM Lung Disease: Clinical Suspicion

- History of Frequent/Recurrent Lung Infections
  - Frequent/Recurrent antibiotic courses to treat Respiratory Infection
  - Early onset of recurrent respiratory infections
- Common co-morbidities:
  - GERD, chronic sinusitis, bronchiectasis (cystic fibrosis, PCD, etc.), COPD, interstitial lung disease, pneumoconiosis, prior TB

National Jewish Health®

Griffith et al. Chest. 2020 Epub ahead of print.

Diagnosis of NTM Lung Disease: Nodular-Bronchiectactic NTM Lung Disease

Epidemiology

- Post-menopausal females (>60 yrs old)
- Scoliosis, mitral valve prolapse, low BMI
- No pre-existing lung disease, CFTR mutation

Clinical course

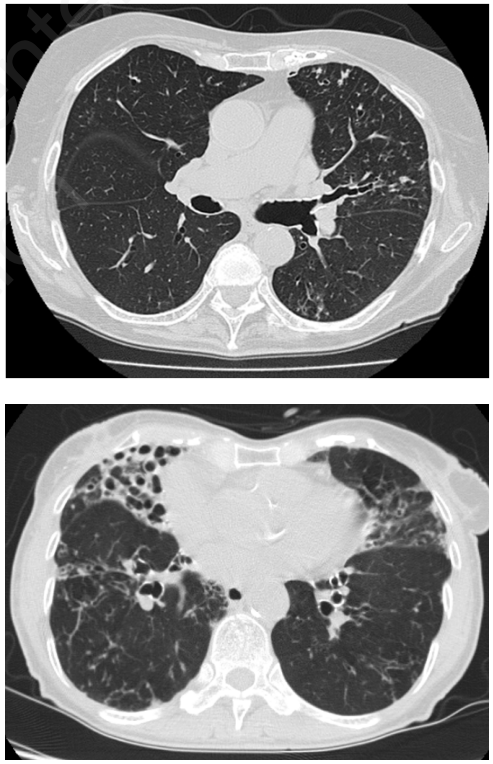
- Prolonged cough, fatigue, weight loss

Microbiology

- Frequently AFB smear negative with culture positivity on broth medium only. Collect multiple sputum specimens or BAL

Radiology: Requires chest CT scan

- Bronchiectasis w/ nodules, tree-in-bud
- Middle lobe and lingula worst affected



'LADY WINDERMERE SYNDROME'

Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
Cowman S et al. Eur Respir J. 2019 Jul 11;54.
Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

National Jewish Health®

Diagnosis of NTM Lung Disease: Fibro-cavitary NTM Lung Disease

Epidemiology

- Mostly male, aged 50-70 yrs old
- Pre-existing COPD, silicosis, fibrosis

Clinical course

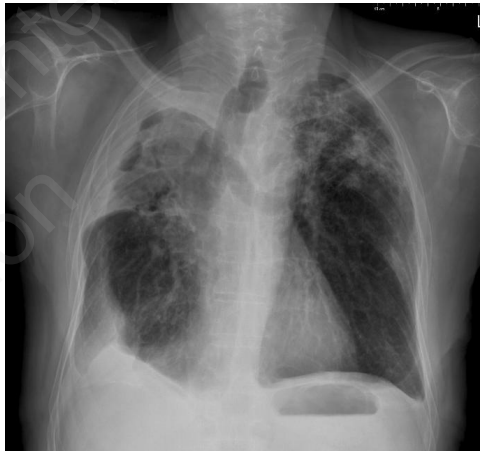
- TB-like, but slower

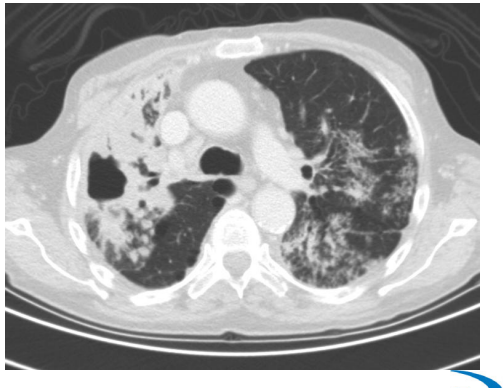
Microbiology

- Often AFB smear positive sputum
- High yield of broth and solid medium culture

Radiology

- Fibro-cavitary lesions, upper lobes: Diagnosis can usually be made on plain chest radiograph





Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
Cowman S et al. Eur Respir J. 2019 Jul 11;54.
Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

National Jewish Health®

Diagnosis of NTM Lung Disease: Microbiology

- Because NTM can be isolated from respiratory specimens due to environmental contamination, the same NTM species (or subspecies in the case of *M. abscessus*) should be isolated in ≥2 sputum cultures.

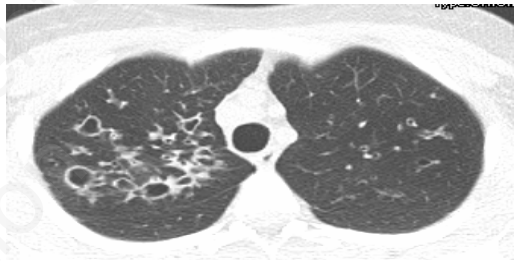
- Clinically significant MAC pulmonary disease is unlikely in patients who have a single positive sputum culture during the initial evaluation but can be as high as 98% in those with ≥2 positive cultures with positive AFB smears.

2020 ATS/IDSA/ERS/ESCMID NTM Statement: CID 2020; 71, 905-913

National Jewish Health®

Diagnostic Protocol for NTM

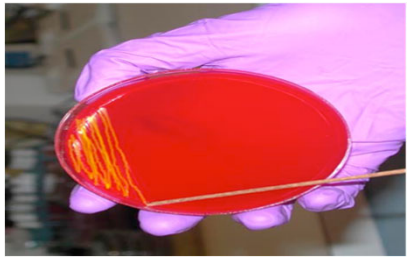
ATS Criteria for NTM Pulmonary Disease



Clinical:

Pulmonary **symptoms**, nodular or cavitary opacities on **CXR or an HRCT** that shows multifocal bronchiectasis with multiple small nodules.

AND



Microbiological:

Positive culture results from at least 2 separate expectorated sputum samples.

OR

Positive culture results from at least 1 BAL

OR

Lung biopsy with mycobacterial or histopathologic features of NTM, with a positive culture for NTM.

National Jewish Health®

2007 ATS/IDSA NTM Statement; Am J Respir Crit Care Med.2007;175:367
2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913

NTM Lung Disease Diagnosis: Plus ca change, plus c'est le meme chose

- No major change in 2020 NTM Document diagnostic criteria c/w 2007 document
- Diagnosis still based on 3 elements: Symptoms, Radiographic findings and Microbiology
- Microbiologic criteria not changed for sputum or bronchoscopy
- Appropriateness of diagnostic criteria still based on NTM species recovered and most relevant for common NTM pathogens, MAC, *M. kansasii, M. abscessus, M. xenopi, M. szulgai, M. malmoense.*
- Diagnostic criteria NOT appropriate for the majority of NTM species that are either not pathogenic for humans or have low virulence, *M. gordonae, M. fortuitum*

2007 ATS/IDSA NTM Statement; Am J Respir Crit Care Med.2007;175:367
2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913

National Jewish Health®

Diagnosis of NTM Lung Disease: Barriers to early diagnosis

- Lack of familiarity with NTM lung disease and/or bronchiectasis including typical patient profiles
- Attribution of patient symptoms, especially cough, to other chronic lung diseases
  - Asthma, chronic bronchitis, COPD (these patients are NON-SMOKERS!)
- Lack of early radiographic assessment
- Delay in ordering AFB analysis for respiratory specimens
- Delay in subspecialty referral

- *Widespread use of chest CT for multiple purposes (scans for cardiac and GI problems) has significantly improved early diagnosis of NTM Lung disease with recognition by radiologists of typical NTM lung disease findings*

National Jewish Health®

Diagnosis of NTM Lung Disease: Key Points

- Clinical suspicion is the most important element for early diagnosis of NTM lung disease.
    - Patient appearance/body morphotype;
    - History of recurrent respiratory infections, typically over years
- Early radiographic assessment:
    - Cough for ***> 8 weeks*** is chronic cough (Irwin R et al. CHEST 2018, 153; 196-209)
    - if patient does not fall into common cough categories (UACS, Asthma, NAEB, GERD), or cough does not resolve with targeted therapy, obtain CXR and/or chest CT
- Obtain respiratory specimens for AFB analysis: spontaneous sputum, induced sputum, bronchoscopy
- Specialist referral

National Jewish Health®

Chapter 3

Management and Treatment Options

National Jewish Health®

Evolution of MAC Therapy

- Prior to 1990, MAC therapy was similar to TB therapy
  - MAC disease diagnosed exclusively in the context of cavitary radiographic changes
- MAC clearly less susceptible *in vitro* to anti-tuberculosis drugs than *M. tuberculosis*
- Treatment regimens frequently included 5-6 anti-tuberculosis drugs including toxic second line drugs like ethionamide and cycloserine
- Outcomes were predictably poor and disappointing.
- So, what happened?

Griffith DE, in Nontuberculous Mycobacterial Disease; Griffith DE (ED) 2019. Pg 1-14.

National Jewish Health®

Evolution of MAC Therapy

- What happened was:
  - Acquired immune deficiency syndrome (AIDS)
    - MAC became the most common bacterial cause of death in AIDS patients
    - Urgent need for better, more effective therapy
  - In 1989, David Prince et al in Philadelphia, first to describe Nodular/Bronchiectatic MAC Lung Disease
  - The MAC lung disease universe significantly expanded

National Jewish Health®

Griffith DE, Nontuberculous Mycobacterial Disease; Griffith DE (ED) 2019. Pg 1-14.

In vitro and *in vivo* activities of clarithromycin against *M. avium*

- MICs for 90% strains 4 mcg/ml
  - MICs for cipro and rifampin also 4 mcg/ml
- Beige mice infected intravenously with *M. avium*
  - Clarithromycin most effective agent tested at reducing viable bacterial counts in the spleen (amikacin the only other agent that showed activity in vivo)

National Jewish Health®

Fernandes PB et al, Abbott Labs, AAC 1989, 33; 1531

In vitro and *in vivo* activities of rifabutin against *MAC*

- Lower MICs against MAC than rifampin *in vitro*
- Active as a single agent against disseminated MAC infection in mice
- Effective prophylaxis against MAC in AIDS patients (improved survival)
- Less severe induction of hepatic microsomal enzymes c/w rifampin, less effect on macrolide blood levels
- BUT….
- Rifabutin is much less well tolerated than rifampin especially in older patients (The critical element for choosing rifampin over rifabutin in NTM Guidelines, no comparative trials for treating MAC).

National Jewish Health®

2007 ATS/IDSA NTM Statement; Am J Respir Crit Care Med.2007;175:367

NTM Drug Resistance: NTM disease is NOT TB

- Innate or “natural” drug resistance
  - Not readily or predictably associated with in vitro measures of resistance such as MICs
  - With 2 exceptions (macrolide/amikacin), *in vitro* susceptibility results do not reliably predict *in vivo* treatment response to antibiotics for MAC lung disease

National Jewish Health®

Van Ingen et al in Nontuberculous Mycobacterial Disease; Griffith DE (ED) 2019. Pg 61-88.

Macrolides and Amikacin for MAC Disease

- Treatment success correlates with in vitro macrolide MIC (susceptible ≤ 8 µg/ml, resistant ≥ 32 µg/ml)
- Treatment success correlates with in vitro amikacin MIC (susceptible ≤ 64 µg/ml, resistant > 64 µg/ml)
- In vitro susceptibility tests for most drugs do not predict who will respond favorably to therapy and who will fail therapy.
- CLSI recommended initial *in vitro* susceptibility testing for initial MAC isolates
  - Macrolide
  - Amikacin

Brown-Elliott B in Nontuberculous Mycobacterial Disease; Griffith DE (ED) 2019. Pg 15-60
CLSI M24, Susceptibility Testing of Mycobacteria, 3rd Ed. Clinical Laboratory Standards Institute, Wayne, PA: 2018)

National Jewish Health®

In vitro antibiotic susceptibility for MAC

- Resistance to macrolides and amikacin emerges when they are not protected by adequate companion medications.
- Protection of macrolides to prevent the emergence of macrolide resistance is a well established priority for clinicians.
- Protection of amikacin is less well appreciated so clinicians must be reminded to use adequate companion medications to prevent the emergence of amikacin resistance.
- Under most circumstances, macrolide and ethambutol would be adequate for protecting amikacin against the emergence of resistance.

National Jewish Health®

Griffith et al. Chest. 2020 Epub ahead of print.

NTM Lung Disease Diagnosis: "Watchful Waiting"

- Meeting diagnostic criteria does NOT automatically require initiating anti-mycobacterial therapy
  - NTM that are contaminants or unusual/rare respiratory pathogens: *M. gordonae*, *M. fortuitum*
  - Patients with MAC who have stable, indolent or slowly progressive disease must be identified by longitudinal follow-up with an open ended duration of follow-up.
- "Watchful waiting" not appropriate for cavitary NTM disease and possibly for some NTM pathogens (*M. kansasii)*

National Jewish Health®

Griffith et al. Chest. 2020 Epub ahead of print

Risk/Benefit of NTM Treatment

Possible "Eradication"
- **70-90% MAC**
- **40-60% *M. abscessus***

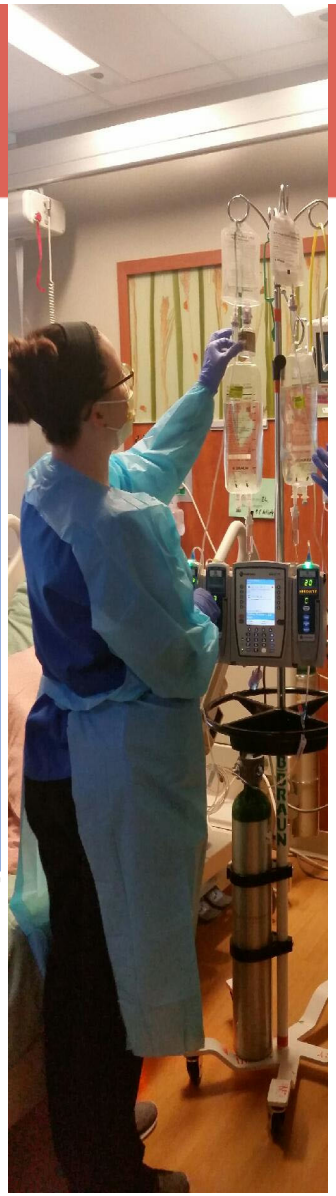
Possible improvement in clinical status (if symptomatic)

Uncertainty over treatment indication

>Year of multi-drug treatment
- **Treatment burden and side-effects**
- **Drug toxicity and side-effects**
- **Complications with IV access**

Uncertainty of response

Possibility of relapse or reinfection



National Jewish Health®

Management and Treatment Options: 2020 NTM Guidelines

- Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?
- In patients who meet the diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect).

National Jewish Health®

(*2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913)*

Management and Treatment Options
Square One: Developing a Treatment Plan

- A patient's adherence with MAC therapy will be greatly facilitated by:
  - the patient's understanding of the disease processes, including bronchiectasis
  - the patient's prognosis,
  - the risks and benefits of therapy (or no therapy),
  - the potential side effects of therapeutic agents and
  - trust that the treating clinician will shepherd the patient through the ups and downs of therapy.
  - In my experience, non-adherence with therapy is unusual, most patients are highly motivated to improve clinically

National Jewish Health®

Should patients with macrolide-susceptible MAC pulmonary disease be treated with a 3-drug regimen with a macrolide or without a macrolide?

- "In patients with macrolide-susceptible MAC pulmonary disease, we recommend a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide."
- Azithromycin preferred over clarithromycin because of better tolerance, less drug-interactions, lower pill burden, single daily dosing, and equal efficacy.
- "In patients with nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, we suggest a 3 times per week macrolide-based regimen rather than a daily macrolide-based regimen".
  - Similar sputum conversion rates, better tolerance intermittent dosing

National Jewish Health®

(2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913)

Should patients with macrolide-susceptible MAC pulmonary disease be treated with a 3-drug regimen with a macrolide or without a macrolide?

- "For patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease, we suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen."
  - Parenteral drug administration for at least 2-3 months of an aminoglycoside [is] the best balance between risks and benefits
- In patients with cavitary or severe/advanced nodular bronchiectatic macrolide-susceptible MAC pulmonary disease we suggest a daily macrolide-based regimen rather than 3 times per week macrolide-based regimen."

National Jewish Health®

(2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913)

Antibiotic Intolerance and Managing Side Effects: General Principles

- Most experts recommend gradual introduction of MAC medications (One week at a time)
- Intermittent (TIW) therapy is better tolerated, in general, than daily therapy with the standard macrolide-based regimen
- There is no persuasive data that daily therapy is more effective than intermittent therapy, with the exception of cavitary disease
- Brief interruptions in therapy do not jeopardize the chances for clinical success
- Splitting doses or taking doses at night may improve medication tolerance
- Taking medications with food may not be optimal but if it allows the patient to tolerate the medication then it is acceptable

Griffith et al. Chest. 2020 Epub ahead of print.
Holt MR et al. In: Griffith DE (Ed), Nontuberculous Mycobacterial Disease; 2019. Pg 310-324.
Cowman S et al. Eur Respir J. 2019 Jul 11;54.
Griffith DE. Semin Respir Crit Care Med. 2018:351-361.

National Jewish Health®

Amikacin liposomal inhalation solution: The most significant change in MAC treatment guidelines between 2007 and 2020

- **ALIS guidelines**: "In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy*, we recommend addition of ALIS to the treatment regimen rather than a standard oral regimen only (strong recommendation, moderate certainty in estimates of effect)."
- **ALIS label**: "ALIS is indicated in adults, who have limited or no alternative treatment options, for the treatment of MAC lung disease as part of a combination anti-bacterial drug regimen inpatients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy….reserve ALIS for use in adults who have limited or no alternative treatment options.

**Failed therapy: persistently positive sputum AFB cultures for MAC after 6 months of guidelines based therapy*.

National Jewish Health®

(*2020 ATS/IDSA/ERS/ESCMID NTM Statement:CID 2020; 71, 905-913)*

Macrolide/Azalide Therapy for Nodular/Bronchiectatic MAC Lung Disease

- Current guidelines for macrolide/azalide-based regimens for NB MAC lung disease result in favorable microbiologic outcomes for most patients
- These regimens do not promote macrolide resistance
- Intermittent regimens as effective as daily regimens with fewer side effects, therefore TIW therapy preferred
- Microbiologic recurrences common, most due to unique MAC genotypes ("reinfection")

National Jewish Health®

Griffith et al. Chest. 2020 Epub ahead of print.

What are the risks for not following NTM Lung Disease treatment guidelines?

Development of Macrolide Resistant MAC

- Risk Factors:
  - Macrolide mono-therapy,
  - Macrolide plus fluoroquinolone
  - Macrolide plus rifampin,
  - Deviation from standard treatment due to adverse effects of ethambutol
  - In one study, 65% treated with guidelines recommended regimens including macrolide/ethambutol/rifamycin

National Jewish Health®

Griffith et al. Chest. 2020 Epub ahead of print.

Why don't clinicians follow published Guidelines for treating NTM Lung Disease?

- Lack of adherence to guideline driven therapy, USA, EU, Japan
  - Adjemian J et al. Ann Am Thorac Soc 2014; 11:9-16
  - Van Ingen J et al. Eur Respir J. 2017;49(2)
- Hard to say why for sure…
- Maybe it's getting better….

National Jewish Health®

Treatment goals

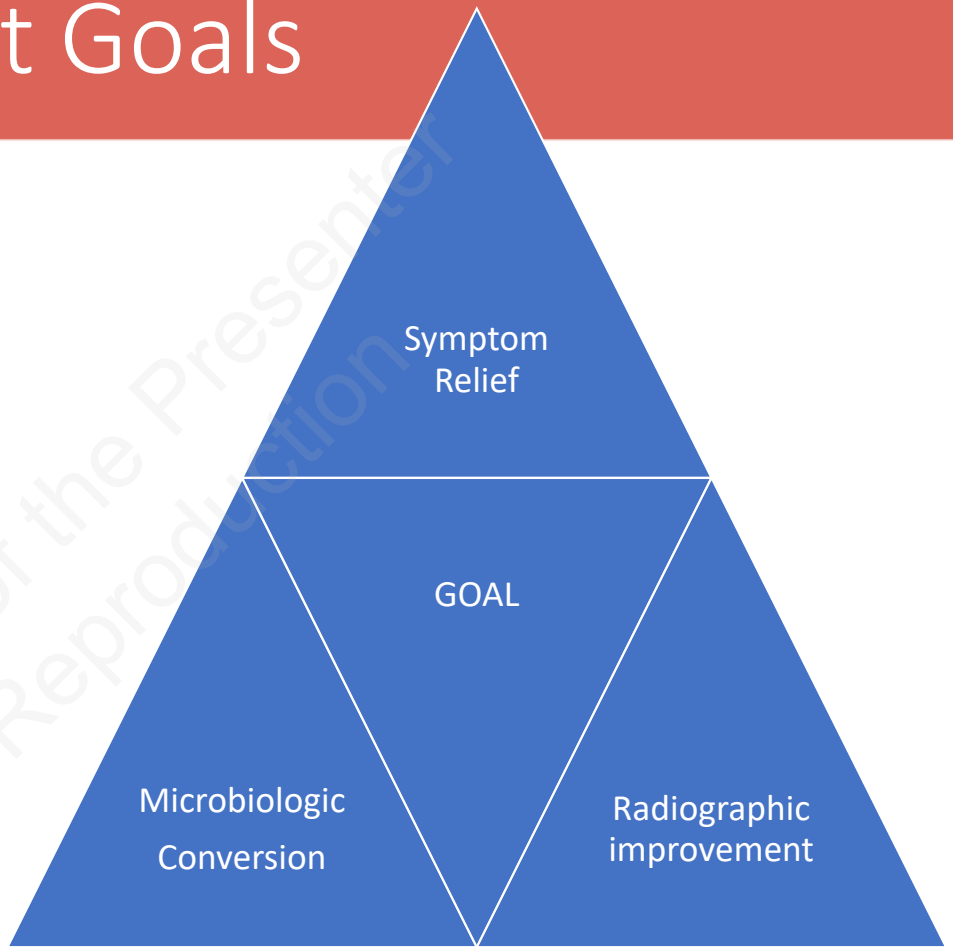
- Cure= 12 months of negative cultures
- Microbiologic conversion: 74% in subjects who could tolerate > 12 mo of treatment

National Jewish Health®

Clin Infect Dis. 2017;65(7):1077.

Treatment Goals

- Share Goals
- Set expectations
- Adverse event education
- Provide verbal & written information
- Provide online resources
  - NTMinfo.org, BronchandNTM360social.org, AboutNTM.com



National Jewish Health®

Common Adverse Reactions and Monitoring Recommendations

Drug	Adverse Reactions	Monitoring
Azithromycin/clarithromycin	• Gastrointestinal • Tinnitus/hearing loss • Hepatotoxicity • Prolonged QTc	• Clinical monitoring • Audiogram • Liver function tests • ECG (QTc)
Ethambutol	• Ocular toxicity • Neuropathy	• Visual acuity/color discrimination • Clinical monitoring
Rifampin/rifabutin	• Hepatotoxicity • Cytopenias • Hypersensitivity • Orange discoloration • Uveitis (rifabutin)	• Liver function test • Complete blood count • Clinical monitoring • Clinical monitoring • Visual acuity
Amikacin/amikacin liposome inhalation suspension (ALIS)	• Oto/vestibular toxicity • Nephrotoxicity • Electrolyte disturbances • Dysphonia (ALIS) • Cough (ALIS) • Dyspnea (ALIS)	• Audiogram • BUN, creatinine • Metabolic panel • Clinical monitoring • Clinical monitoring • Clinical monitoring/PFTs

Patient monitoring

Monthly

Lab work

Sputum culture

Audiogram (IV AK)

Every three months

Clinical monitoring

Vestibular testing

Eye exam

Spirometry

Every six months

CT imaging (low dose)

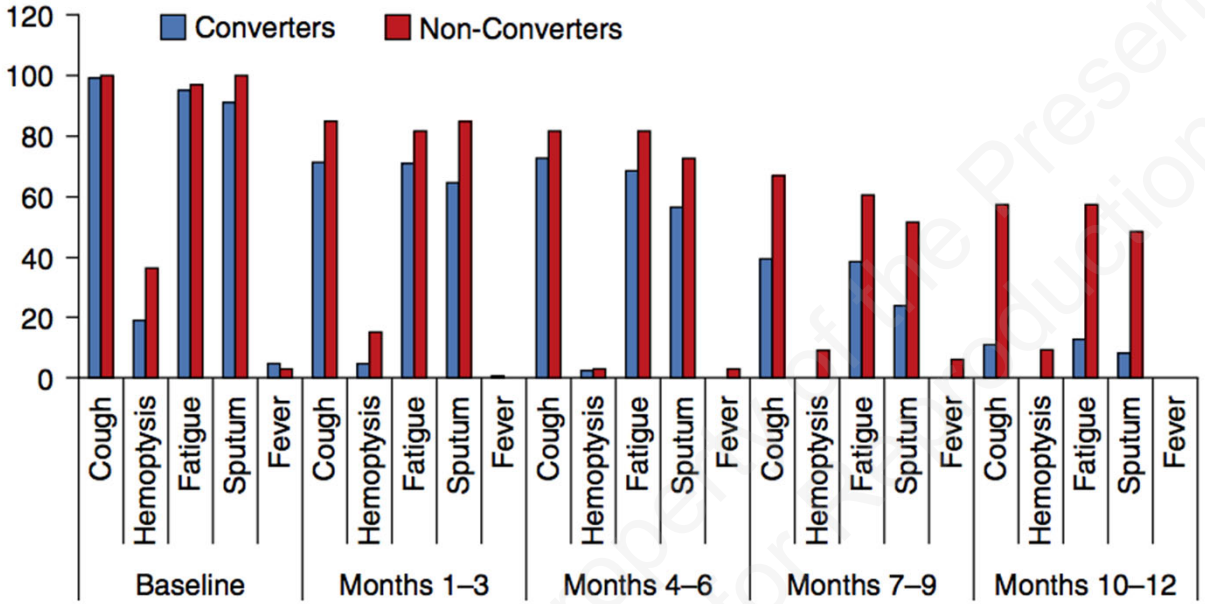
ECG

Audiogram

Review airway clearance

National Jewish Health®

Symptomatic response to therapy



Early semiquantitative sputum agar plate culture results can be used to predict symptomatic and radiographic improvement as well as long-term sputum culture conversion to negative

Griffith D et al. *American journal of respiratory and critical care medicine*. 2015, Vol.192(6), p.754-760.
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

National Jewish Health®

Summary

- Thrice weekly therapy for NON-severe bronchiectatic nodular macrolide susceptible disease
- Cavitary or severe disease is treated with daily oral therapy + IV aminoglycoside for the first 2-3 months
- A goal of 12 months of negative cultures requires sputum cultures every 1-2 months
- Begin airway clearance and consider hypertonic saline therapy at home
- ALIS should be used in treatment refractory disease (culture + at 6 mo)

National Jewish Health®

Chapter 4

Cases

National Jewish Health®

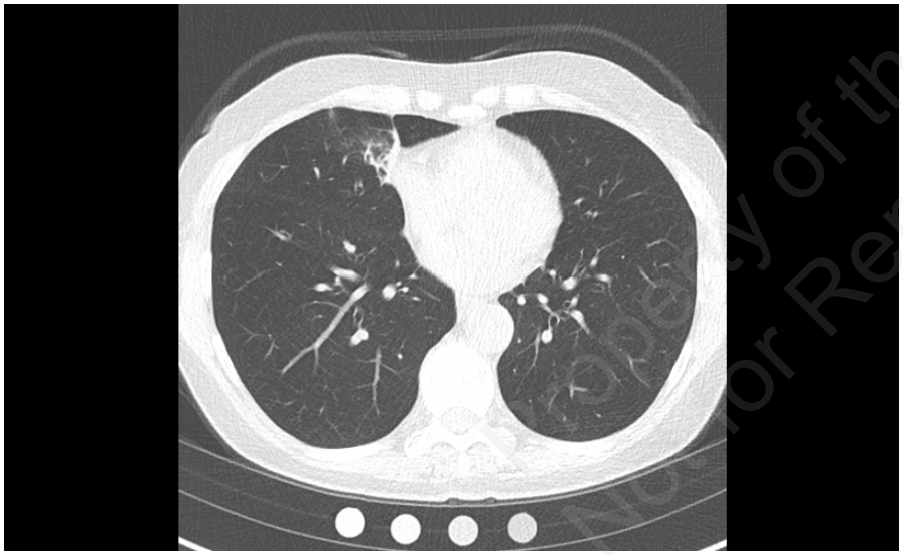
MAC Management: Stable Disease, Watchful Waiting

- 68 year old nonsmoking female with history of frequent respiratory infections, chronic cough, sputum production, fatigue and weight loss
- Diagnosed with bronchiectasis, GERD only identified predisposition
- 6/2020 to 10/2020: 2/5 sputum specimens AFB smear negative, culture positive for MAC, liquid media only
- Patient instructed in airway clearance measures
- 10/2020 to 3/2021: Symptomatically better, 3/3 sputum AFB smears and cultures negative
- 6/2020 to 3/2021: 2/8 sputum AFB smears and cultures positive, liquid media only

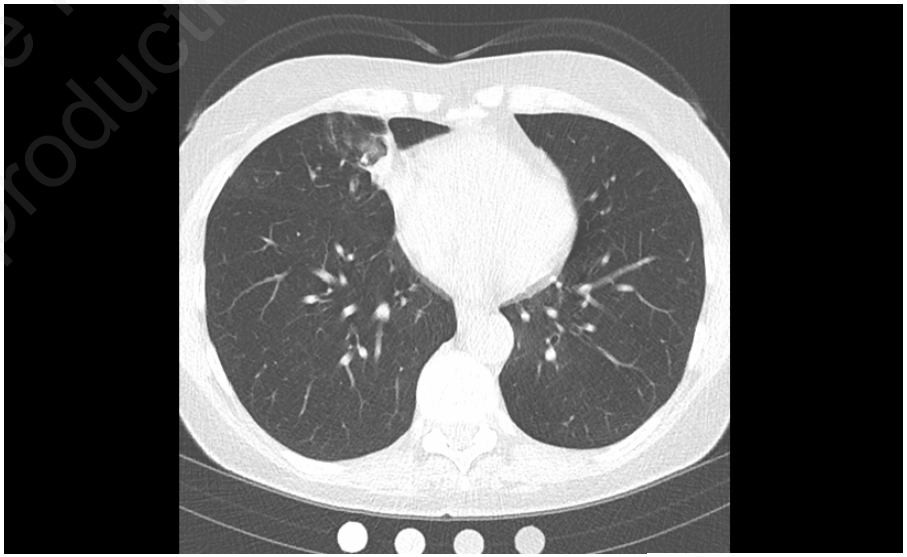
National Jewish Health®

MAC Management: Stable Disease, Watchful Waiting

6/2020 to 10/2020, 2/5 Sputum AFB cultures positive, liquid media only



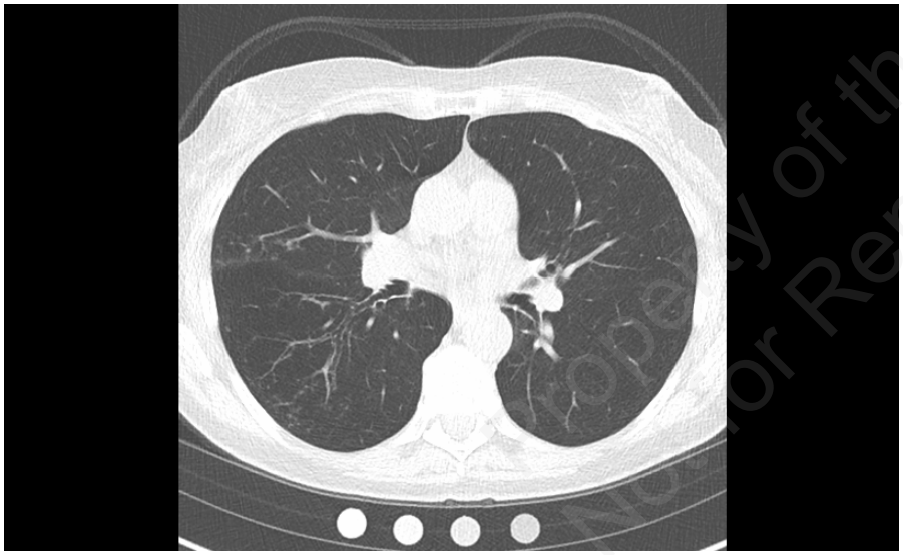
10/2020 to 3/21, 3/3 Sputum AFB cultures negative (2/8 Positive liquid media only)



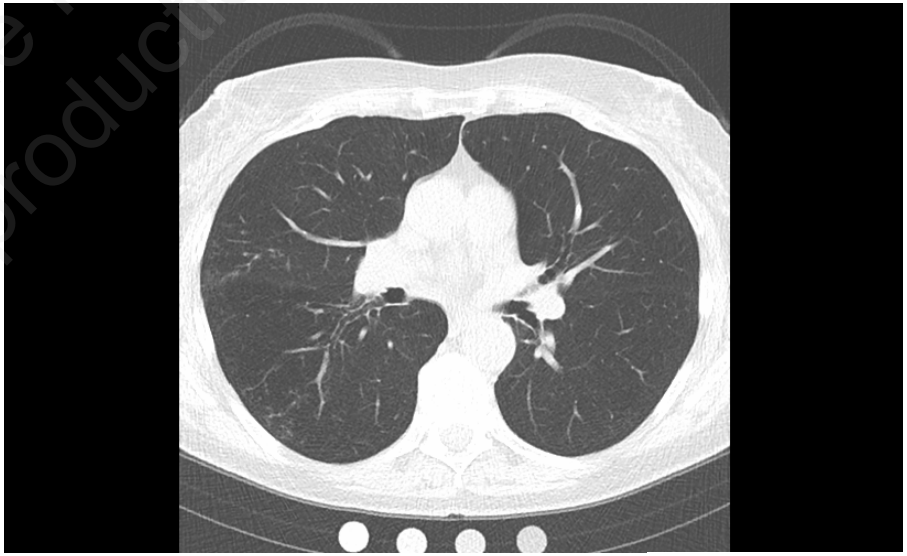
National Jewish Health®

MAC Management: Stable Disease, Watchful Waiting

6/2020 to 10/2020, 2/5 Sputum AFB cultures positive, liquid media only



10/2020 to 3/21, 3/3 Sputum AFB cultures negative (2/8 Positive liquid media only)



National Jewish Health®

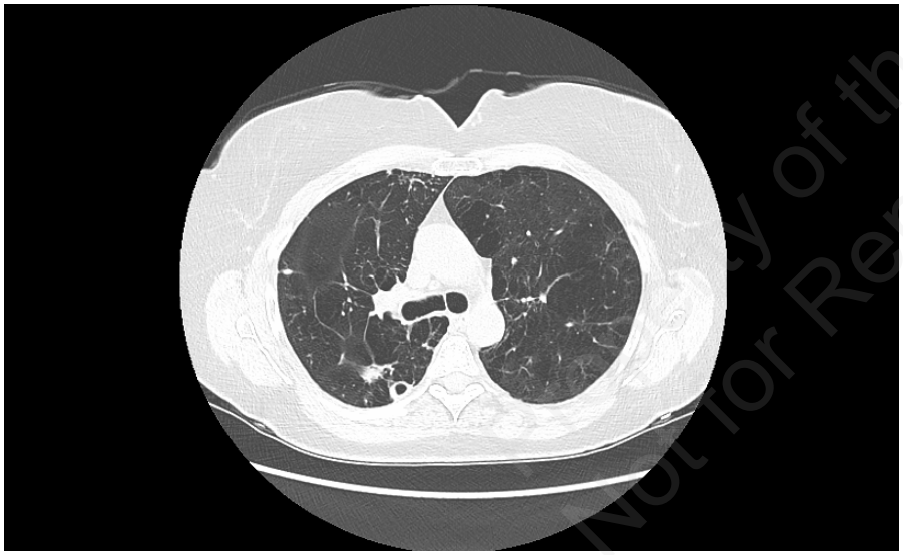
MAC Management: Initial Guidelines-Based Therapy

- 55 years old female, ex-smoker (20 pack years) diagnosed with MAC Lung Disease 2019
- Patient with recurrent pneumonia, chronic cough and sputum production, fatigue, weight loss and episodic hemoptysis
- Multiple sputum specimens AFB culture positive for macrolide/amikacin susceptible MAC
- Started azi/emb/rmp TIW 4/19 with conversion of sputum to AFB culture negativity in 8/19
- Symptomatic and radiographic improvement with one year of negative sputum AFB cultures while on MAC therapy

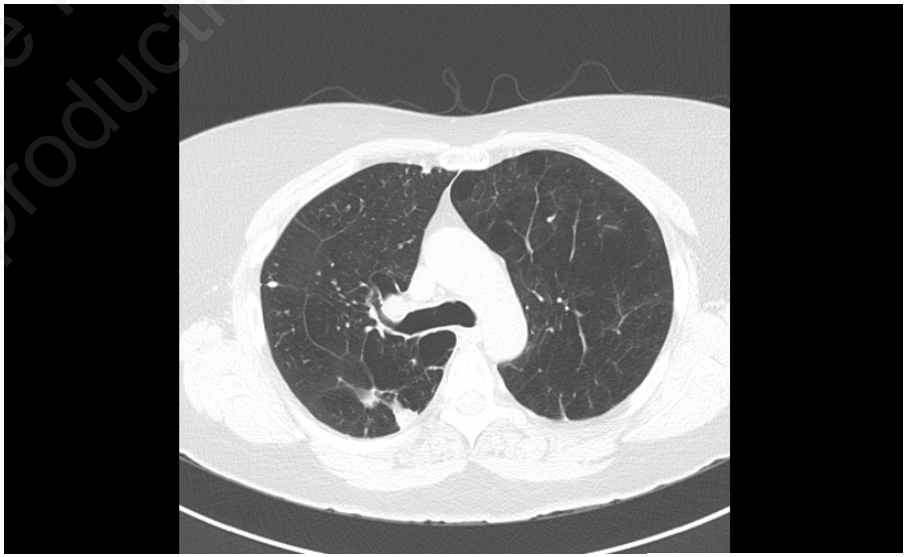
National Jewish Health®

MAC Management: Initial Guidelines-Based Therapy

4/19 Multiple sputum AFB cultures positive for MAC, symptomatic



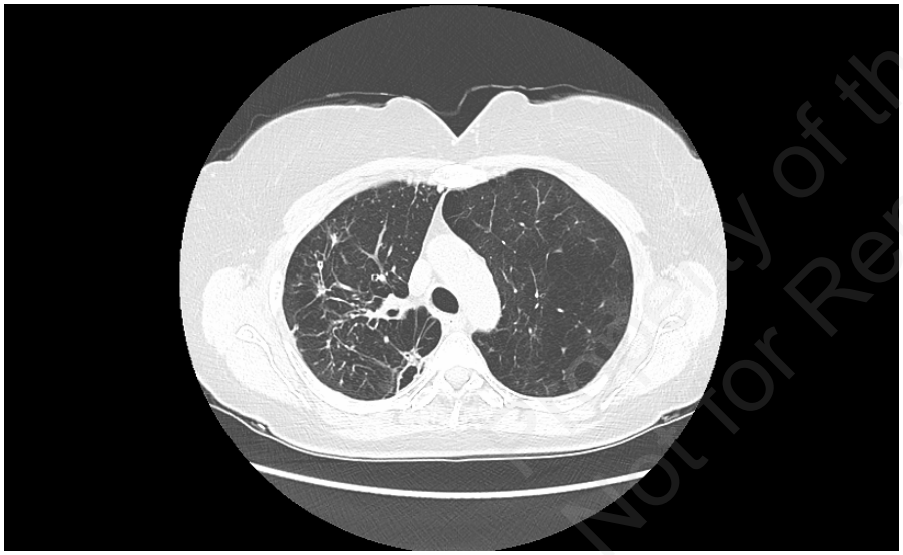
8/2020 Negative sputum cultures for 12 months on azi/emb/rmp, symptoms improved



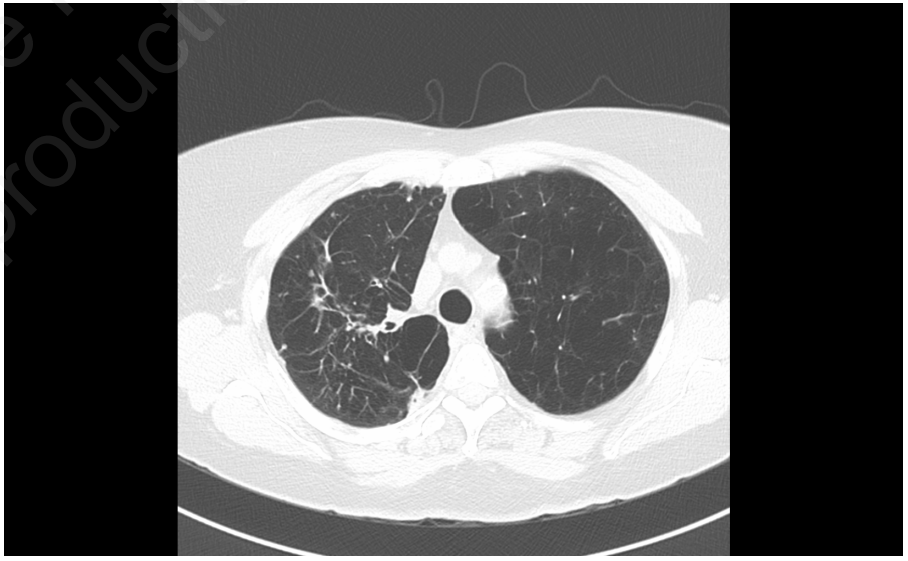
National Jewish Health®

MAC Management: Initial Guidelines-Based Therapy

4/19 Multiple sputum AFB cultures positive for MAC, symptomatic



8/2020 Negative sputum cultures for 12 months on azi/emb/rmp, symptoms improved



National Jewish Health®

Case Treatment refractory

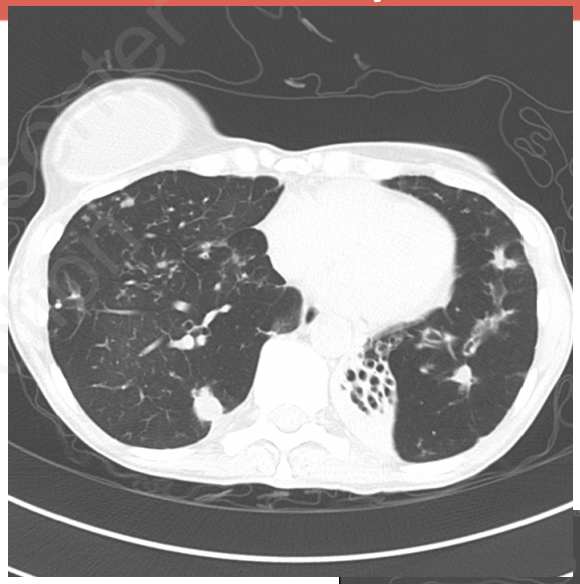
65 year old female, lifelong non-smoker

2007 developed recurrent bronchitis and pneumonia
2008 CT scan noting LLL bronchiectasis and scattered nodularity
BAL + MAC

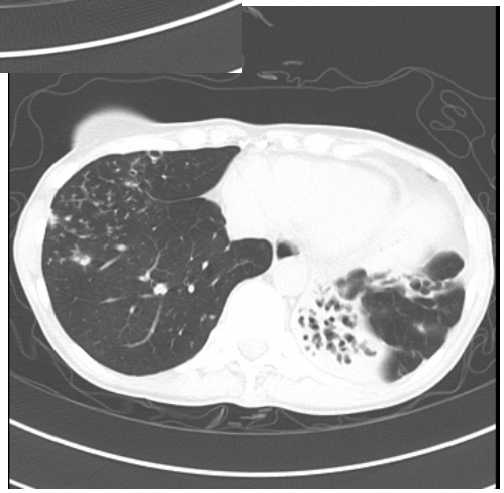
2008-2011 Clarithromycin + ethambutol + rifampin daily
-recurrent bronchopulmonary infections ceased
-? Culture clearance

2015 Cough gradually returns and fatigue develops
2016 “I was so fatigued I could barely move around the house”
Sputum cultures + MAC, macrolide sensitive

2016 Started back on clarithromycin + ethambutol + rifampin

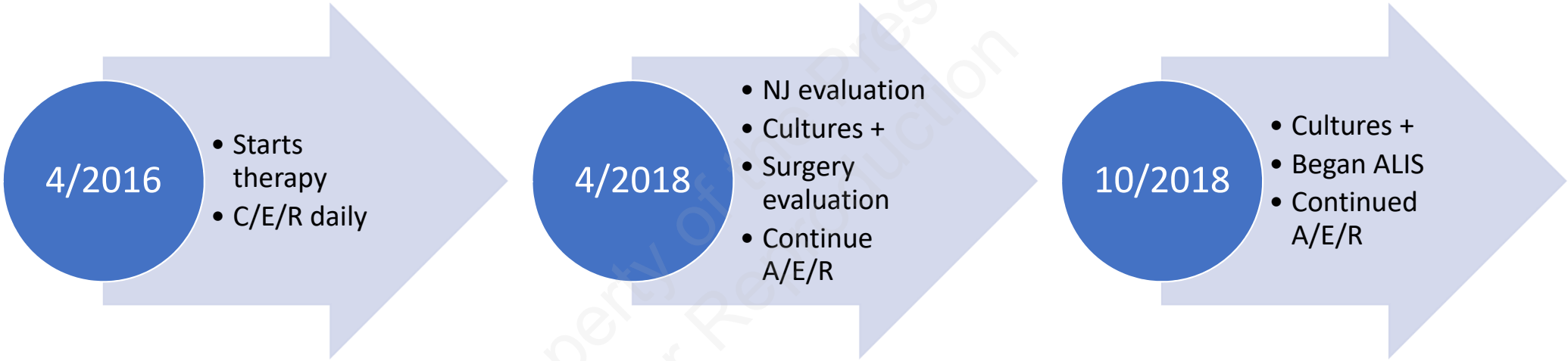


April 2016



National Jewish Health®

Case Treatment refractory

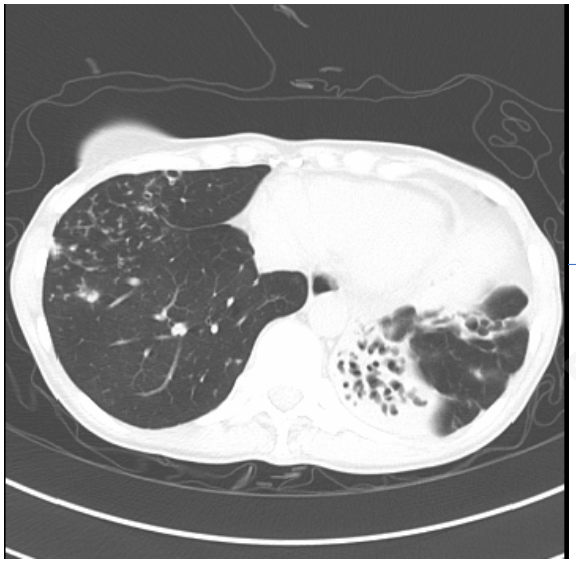


National Jewish Health®

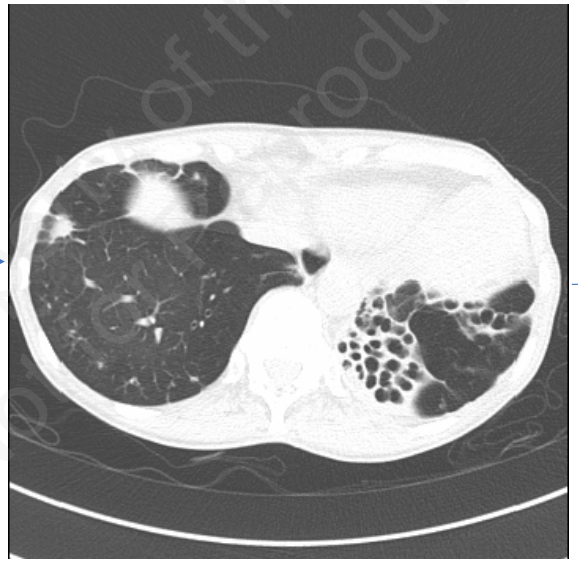
Case Treatment refractory

After beginning ALIS, patient was able to achieve 12 months of negative cultures
She ended treatment in 10/2019.
Cultures remain negative 18 months off treatment (submits q 3 mo)

2016: beginning of treatment



2019: end of treatment



2021: 18 months off treatment