PILOT™ Education Transforming PULMONARY CARE

A Team Based Approach for Improving

NTM-LD

Diagnosis & Management

Provided by The France Foundation

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Educational Support

This educational activity is supported by an educational grant from Insmed.

Learning Objectives

- Describe key steps in NTM-LD diagnosis and how to reduce time to patient identification
- Incorporate practice guidelines, the latest evidence, and a multidisciplinary approach into management strategies for NTM-LD patients
- Assess how individualized treatment plans may help to further address complex cases of NTM-LD

Case 1

- 63-year-old female, originally from Korea but in the US for more than 30 years with occasional trips back to South Korea. Referred by her PMD because of recurrent respiratory tract infection
- She has been having recurrent episodes of cough with productive sputum for at least the last 4-5 years. She responds to courses of azithromycin but then recently, her episodes have become more frequent.
- These episodes have not been associated with fevers but recently has experienced weight loss which prompted her physician to obtain CT of the chest, abdomen, and pelvis and then referred her to ID because of abnormal CT scan

Past Medical History/Social History/ Medications

- GERD
- Osteopenia
- Depression/Anxiety
- Hyperlipidemia

- Medications:
  - Pantoprazole
  - Escitalopram
  - Atorvastatin

- Social History
  - Has never smoked
  - Does not consume alcohol or recreational drugs
  - Worked as a special education teacher

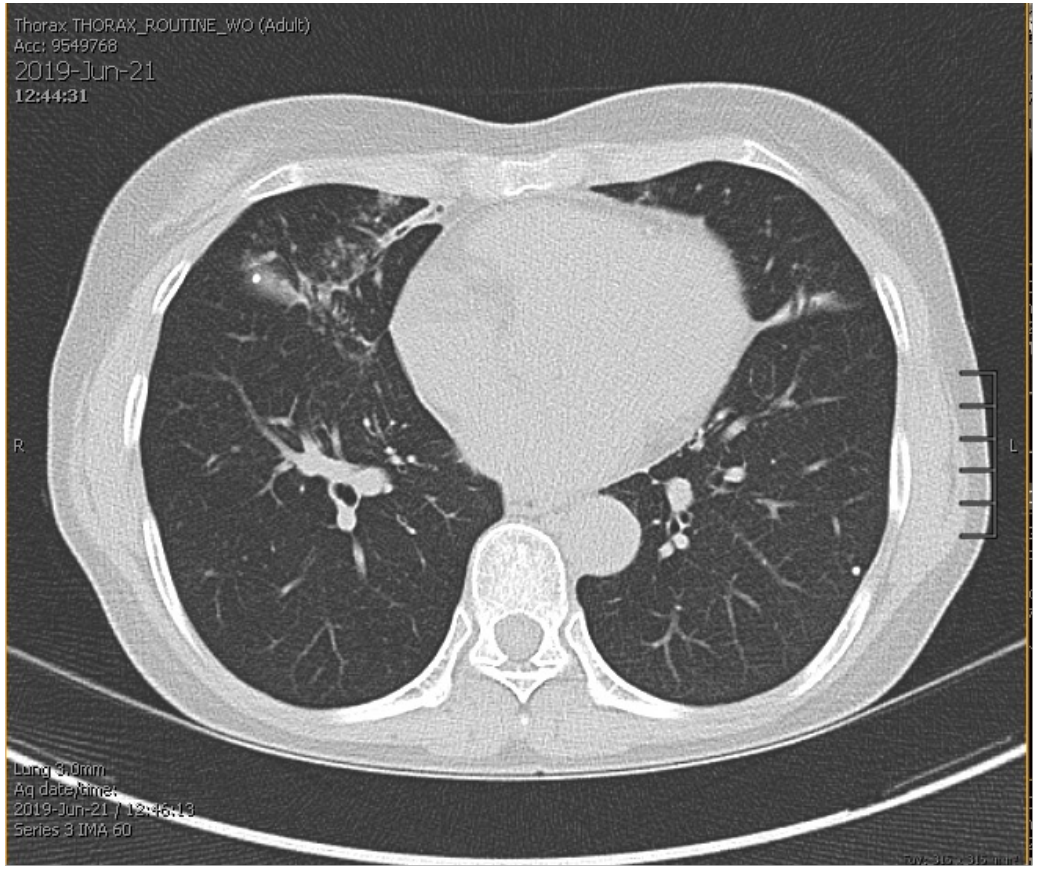
GERD, gastroesophageal reflux disease

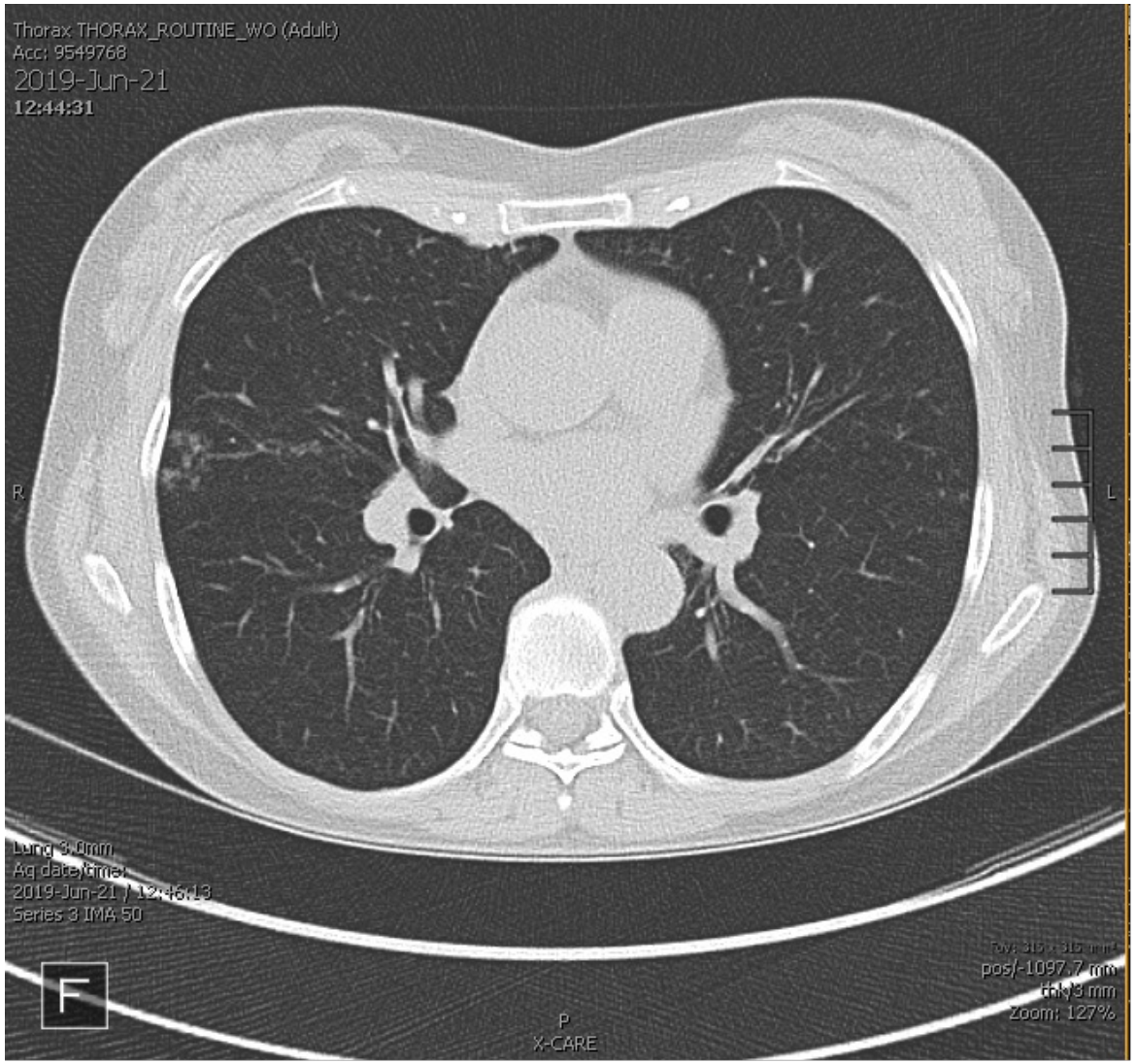
Physical Exam/CT Scan Findings/Further Workup

- She is afebrile, nontoxic, and her physical exam is normal except for a BMI of 22
- Workup:
  - CBC, CMP were normal
  - T-SPOT Negative
  - AFB Smear: Positive on 8/1/2019; Started on MTB Treatment

CBC, complete blood count; CMP, comprehensive metabolic panel; T-SPOT, tuberculosis test; AFB, acid- fast bacilli

Case 1–Baseline CT





- CT Scan on 6/21/2019 shows:
  Areas of mild consolidation in the lingula and the right middle lobe with bronchiectasis and tree-in-bud nodularity in both of these regions as well as the inferior right upper lobe.

Scans courtesy of P. Kumar

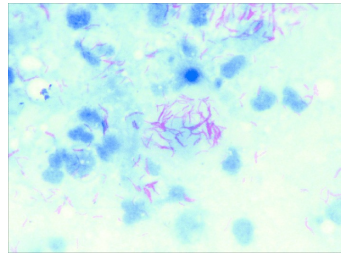
Common Mycobacterial Species Causing Disease

- Mycobacterium Tuberculosis Complex
  - *M. Tuberculosis*
  - *M. Bovis*
  - *M. africanum*
- Mycobacterium leprae
- Rapidly growing nontuberculous mycobacteria
  - *M. fortuitum complex*
  - *M. chelonae*
  - *M. abscessus*
  - *M. smegmatis*
  - *M. mucogenicum*
- Slow growing nontuberculous mycobacteria
  - *M. kansasii*
  - *M. marinum*
  - *M. gordonae*
  - *M. scrofulaceum*
  - *M. avium complex*
    - *M. avium*
    - *M. intracellulare*
    - *M. Chimaera*
    - *(others)*

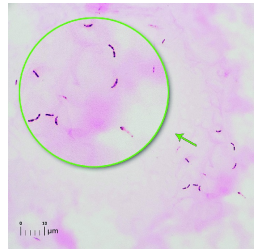
Nontuberculous Mycobacteria That Most Commonly Cause Lung Disease

- ***Mycobacterium avium* complex (*MAC*)**
- ***Mycobacterium kansasii***
- ***Mycobacterium xenopi***
- ***Mycobacterium abscessus***

Laboratory Diagnosis of Mycobacteria



Ziehl-Neelsen[1]



Kinyoun[2]

- Acid Fast Smear is done by either Ziehl-Neelsen or Kinyoun
- AFB Culture:
  - —Solid medium: Lowenstein-Jensen and agar Middlebrook 7H10 or 7H11
  - —Liquid medium: Mycobacteria growth indicator tube (MGIT)
  - —Can take 4-6 weeks to grow
  - —To identify mycobacteria, conventional biochemistry tests are used
- Early identification utilizes DNA probes
  - — *M. tuberculosis* complex culture identification test—Rapid DNA Probe
  - — *MAC* Culture Identification Test—Rapid DNA Probe

1. Prasad CSBR, et al. *Ann Trop Med Public Health*. 2011;4:110-112.
2. van de Weg CAM, et al. *Access Microbiol*. 2019;2(1):acmi000074.

Decreasing Time to Diagnosis:

- "Time is tissue"
  - Time to diagnosis of NTM-LD can be as long as 3-5 years
  - Diagnostic delays often lead to destruction of lung tissue
- Clinical presentation is often nonspecific
  - Need to have a high index of suspicion
  - Consider NTM in patients who present with persistent cough and nonspecific symptoms, especially if present for more than 6 weeks
- Sputum samples
  - Multiple samples should be obtained/tested (ideally ≥3)
  - Send specifically for AFB Smear and Culture

Ryu YJ et al. *Tuberc Respir Dis.* 2016;79:74-84; Young JD et al. *J Respir Dis.* 2007;28:7-18

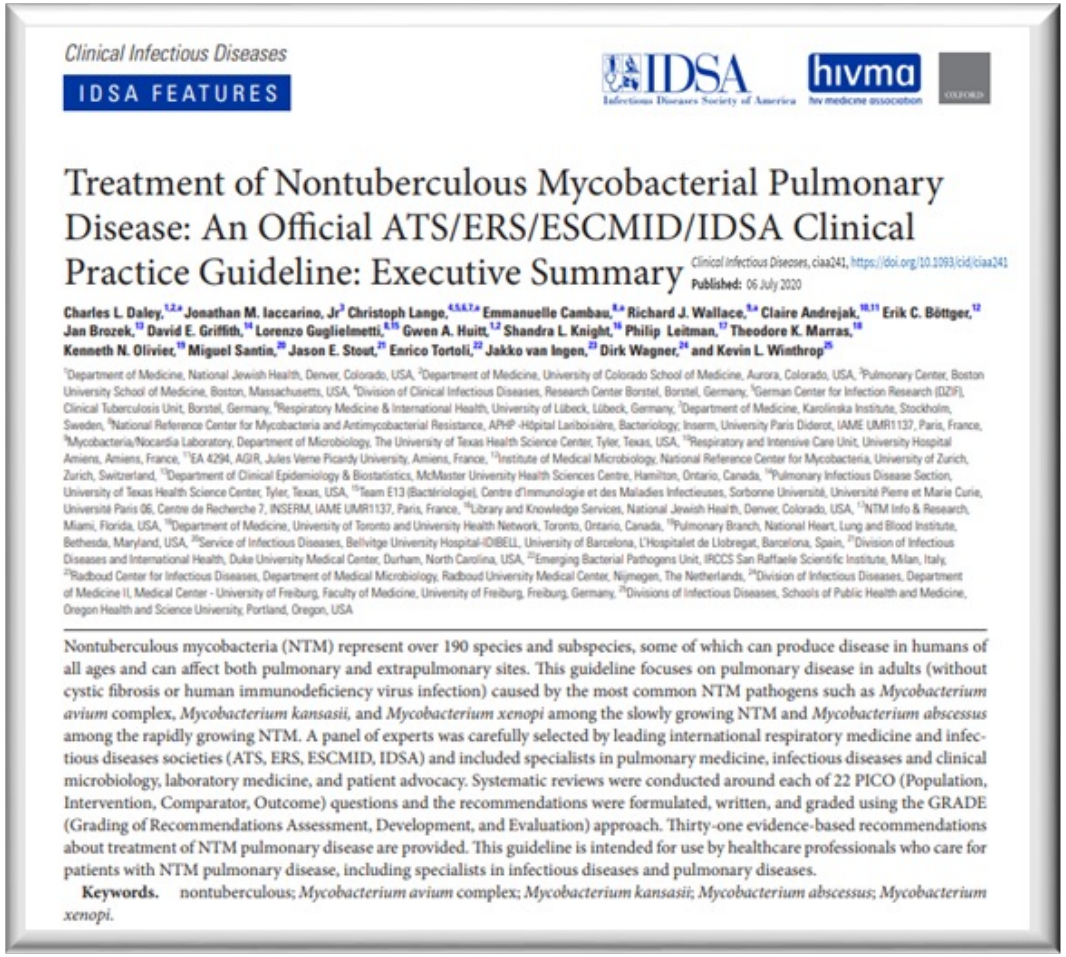
Case 1–Culture Results

- Cultures grew out *MAC* from 8/1/2019
- Repeat AFB Sputum smear and culture done on 8/12/2019
  - —AFB Smear Positive
  - —Culture positive for *MAC*
- Repeat AFB Sputum smear and culture done on 8/22/2019
  - —AFB Smear Positive
  - —Culture positive for *MAC*

2020 ATS/ERS/ESCMID/IDSA Clinical Practice Guideline for NTM Pulmonary Disease

What Has Not Changed?

- Criteria for diagnosis (+ cultures + radiographs + symptoms)
- Duration of therapy (12 months of negative cultures while on therapy)
- Not all patients who meet diagnostic criteria require treatment (**guidelines suggests initiation of therapy over watchful waiting, especially with risk factors**)



Clinical Infectious Diseases

IDSA FEATURES

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline: Executive Summary

Clinical Infectious Diseases, ciaa241, https://doi.org/10.1093/cid/ciaa241
Published: 06 July 2020

Charles L. Daley, Jonathan M. Iaccarino, Jr, Christoph Lange, Emmanuelle Cambau, Richard J. Wallace, Claire Andrejak, Erik C. Böttger, Jan Brozek, David E. Griffith, Lorenzo Guglielmetti, Gwen A. Huitt, Shandra L. Knight, Philip Leitman, Theodore K. Marras, Kenneth N. Olivier, Miguel Santin, Jason E. Stout, Enrico Tortoli, Jakko van Ingen, Dirk Wagner, and Kevin L. Winthrop

Nontuberculous mycobacteria (NTM) represent over 190 species and subspecies, some of which can produce disease in humans of all ages and can affect both pulmonary and extrapulmonary sites. This guideline focuses on pulmonary disease in adults (without cystic fibrosis or human immunodeficiency virus infection) caused by the most common NTM pathogens such as *Mycobacterium avium* complex, *Mycobacterium kansasii*, and *Mycobacterium xenopi* among the slowly growing NTM and *Mycobacterium abscessus* among the rapidly growing NTM. A panel of experts was carefully selected by leading international respiratory medicine and infectious diseases societies (ATS, ERS, ESCMID, IDSA) and included specialists in pulmonary medicine, infectious diseases and clinical microbiology, laboratory medicine, and patient advocacy. Systematic reviews were conducted around each of 22 PICO (Population, Intervention, Comparator, Outcome) questions and the recommendations were formulated, written, and graded using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Thirty-one evidence-based recommendations about treatment of NTM pulmonary disease are provided. This guideline is intended for use by healthcare professionals who care for patients with NTM pulmonary disease, including specialists in infectious diseases and pulmonary diseases.

Keywords. nontuberculous; *Mycobacterium avium* complex; *Mycobacterium kansasii*; *Mycobacterium abscessus*; *Mycobacterium xenopi*.

Daley CL, et al. *Clin Infect Dis/Eur Respir J.* 2020;71(4):e1-e36.

2020 NTM Diagnostic Guidelines Essentially Unchanged

Disease Criteria (unchanged from 2007 guidelines)	
Clinical	Pulmonary/systemic symptoms
Radiology	CXR-nodules, cavities, or CT-bronchiectasis with multiple small nodules
Micro	With ≥ 2 sputa → 2 positive cultures, or With 1 BAL/wash → 1 positive bronchial wash, or With biopsy → positive biopsy culture, or 1 positive culture and biopsy evidence of disease

Symptoms + Imaging findings + Microbiology = Disease…

…deciding to initiate antimicrobial therapy for NTM-PD should be individualized based on clinical factors, the infecting species, and individual patient priorities. Decision should include a discussion with the patient that outlines the potential side effects of antimicrobial therapy, the uncertainties surrounding the benefits of antimicrobial therapy, and the potential for recurrence including reinfection.

Daley CL et al. *Clin Infect Dis/Eur Respir J.* 2020;71(4):e1-e36.

Suggesting Treatment Versus Watchful Waiting

Natural history

- Unpredictable
- Majority progress
- Minority spontaneously convert to negative sputum

Question: Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?

Answer: In patients who meet diagnostic criteria for NTM-PD, **guidelines suggest initiating treatment rather than watchful waiting**. Especially in the context of positive AFB smears and/or cavitation (conditional recommendation, very low confidence in estimates of effect).

Daley CL, et al. *Clin Infect Dis/Eur Respir J.* 2020;71(4):e1-e36.

Risk Factors for Pulmonary Nontuberculous Mycobacterial Disease

- Underlying lung architectural abnormalities[1]
  - Bronchiectasis, cystic fibrosis, emphysema[1,3]
  - α-1 antitrypsin
  - Prior history of TB
  - GERD with micro-aspiration
- Patient Characteristics (Lady Windermere Syndrome)[2]
  - Female Sex
  - Scoliosis
  - Pectus Escavatum
  - Mitral valve prolapse
- Immunodeficiency[2]
  - IFN-ɣ and IL-12 defects
  - Anti–TNF-α therapy
  - Steroid therapy
- Exposure[1]
  - Hot Tubs
  - Gardening
  - Other

1. Daley CL, et al. *Clin Infect Dis*. 2020;71:e1-e36.
2. Johnson MM, Odell JA. *J Thorac Dis*. 2014;6(3):210-220.
3. Griffith DE, et al. *Am J Respir Crit Care Med*. 2007;175(4):367-416.

Risk Factors Associated With Progression of NTM-PD

Host/demographic	Laboratory
• Male sex • Younger age • Presence of comorbidities • Low body mass index	• Elevated inflammatory indices (ESR, CRP) • Anemia • Hypoalbuminemia
Radiographic	**Microbial**
• Fibrocavitary disease • Extent of disease	• Bacterial load • Species

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Daley CL, Winthrop KL. *J Infect Dis.* 2020; 222 (Suppl 4):S199–S211.

Case 1 Susceptibility Testing Results

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
MAC Susceptibility Broth					
Organism ID					
Mycobacterium avium complex	**Abnormal**				01
Amikacin					
	8.0 ug/mL	Susceptible			01
Ciprofloxacin	>8.0 ug/mL				01
Clarithromycin					
	1.0 ug/mL	Susceptible			01
Doxycycline	>8.0 ug/mL				01
Linezolid					
	8.0 ug/mL	Susceptible			01
Minocycline	8.0 ug/mL				01
Moxifloxacin					
	>4.0 ug/mL	Resistant			01
Rifabutin	0.5 ug/mL				01
Rifampin	2.0 ug/mL				01
Streptomycin	16.0 ug/mL				01
Trimethoprim/Sulfa	2/38 ug/mL				01

Pulmonary MAC

Drug susceptibility testing

Interpretation is unclear for most drugs, except…

Macrolides:

- Resistance (clarithromycin MIC ≥ 32 mcg/mL) → poor response/outcomes

Amikacin (IV)

- Susceptible MIC ≤ 16 mcg/mL
- Intermediate MIC 32 mcg/mL
- Resistant MIC ≥ 64 mcg/mL

Amikacin Liposomal Inhalation

- Susceptible MIC ≤ 64 mcg/mL
- Resistant MIC ≥ 128 mcg/mL

Resistance associated with treatment failure despite amikacin administration

Brown-Elliot BA et al. *J Clin Microbiol.* 2013;51(10):3389-3394.

RCT of inhaled amikacin → no patients with isolate MIC > 64 converted sputum

Olivier KN et al. *Am J Respir Crit Care Med.* 2017;195(6):814-823.

Genesis Study: Ethambutol Is Critical for Reducing Risk of Macrolide Resistance

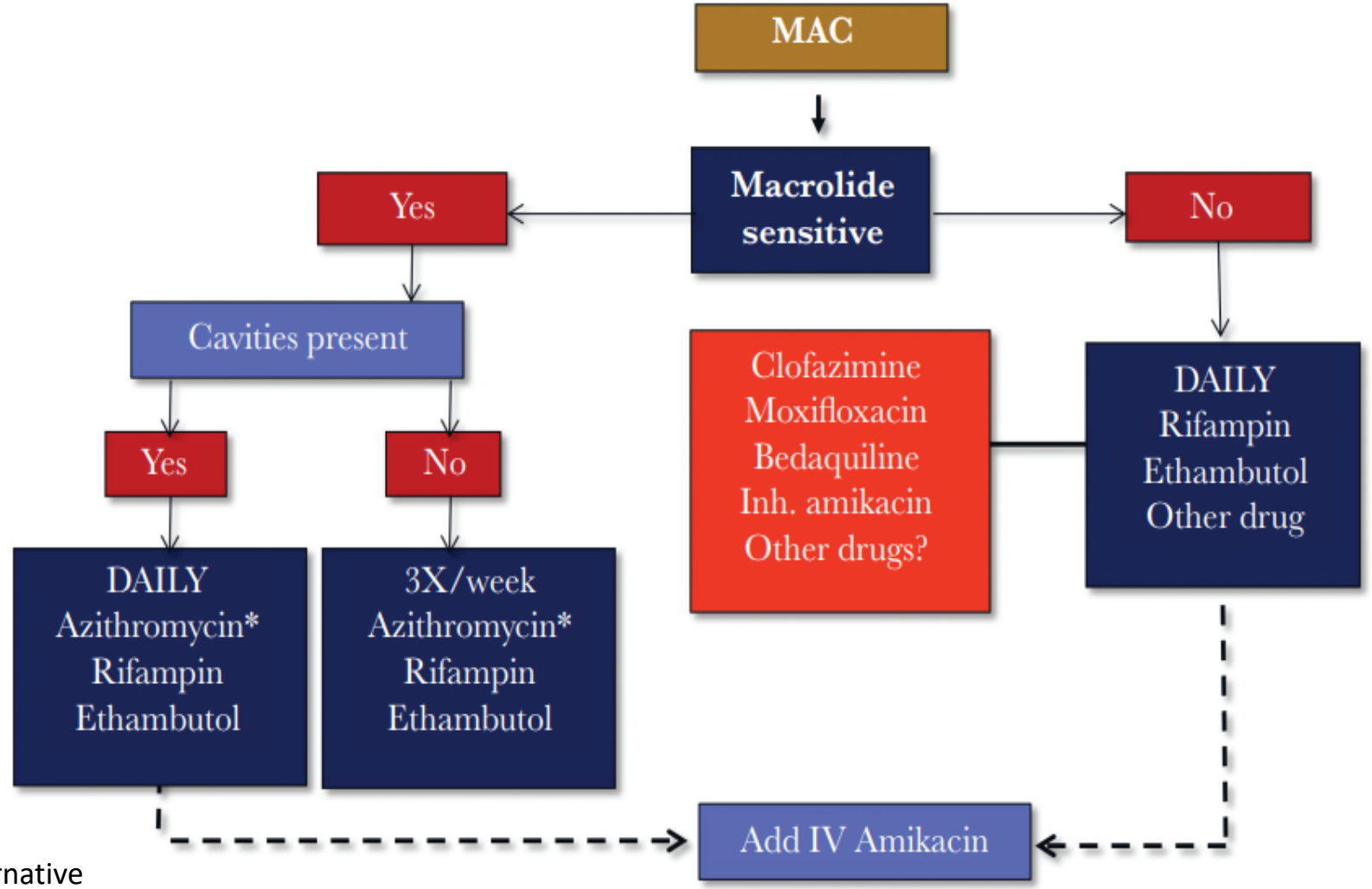
- Observational study of MAC lung disease (non-HIV)[1]
  - 4 months of macrolide monotherapy → 20% resistance
  - Initial macrolide/rifamycin/ethambutol → 4% resistance
- 134 patients with macrolide resistance and known prior treatment history[1,2]

Prior Treatment	Number (%)
Macrolide monotherapy	57/134 (43%)
Macrolide/fluoroquinolone	17/134 (13%)

- *Ethambutol appears to be the critical companion drug for reducing the risk of macrolide resistance*

1. Griffith DE, et al. *Am J Respir Crit Care Med*. 2006;174:928-934.
2. Morimoto K, et al. *Ann Am Thorac Soc*. 2016;13:1904-1911.

MAC-PD Treatment Algorithm



*clarithromycin is an alternative
Inh, inhaled

Daley CL, Winthrop KL. *J Infect Dis*. 2020; 222 (Suppl 4):S199–S211.

Duration: 12 mos culture negativity

Monitoring While on Treatment

- Microbiological monitoring:
  - Obtain sputum cultures every one to two months following treatment initiation to monitor treatment efficacy
    - The duration of treatment is 12 months from sustained negative cultures
    - Once sustained conversion has been achieved, sputum cultures can be obtained less frequently
- Radiographic monitoring
- Monitoring for side effects of the medications

Monitoring for Side Effects

- Patients are best managed via multidisciplinary team given the frequency of adverse reactions
  - ~20-37% of patients with pulmonary MAC discontinue therapy
- Common Side effects requiring monitoring

Side Effect	Clarithro-mycin	Azithro-mycin	Rifampin	Clofazimine	Rifabutin	Etham-butol	Amino-glycosides*	Macro-lides	Fluoro-quinolones
Gastrointestinal intolerance	✓	✓	✓	✓					
Abnormal liver function tests	✓	✓	✓						
Low white blood cell count			✓		✓				
Impaired visual acuity or color vision						✓			
Decreased auditory function		✓					✓		
Vestibular toxicity							✓		
Decreased renal function							✓		
Peripheral neuropathy				✓		✓	✓		
Prolonged QTc				✓				✓	✓

*Systemic or inhaled

UpToDate: Kasperbauer S, Daley CL. Treatment of Mycobacterium avium complex pulmonary infection in adults.

Importance of a Multidisciplinary Team

- The frequency of adverse events makes responsiveness of and trust in the clinical team critical
  - Best achieved through a multidisciplinary team
- Educating patients on the importance airway clearance

Case 1–Treatment Regimen

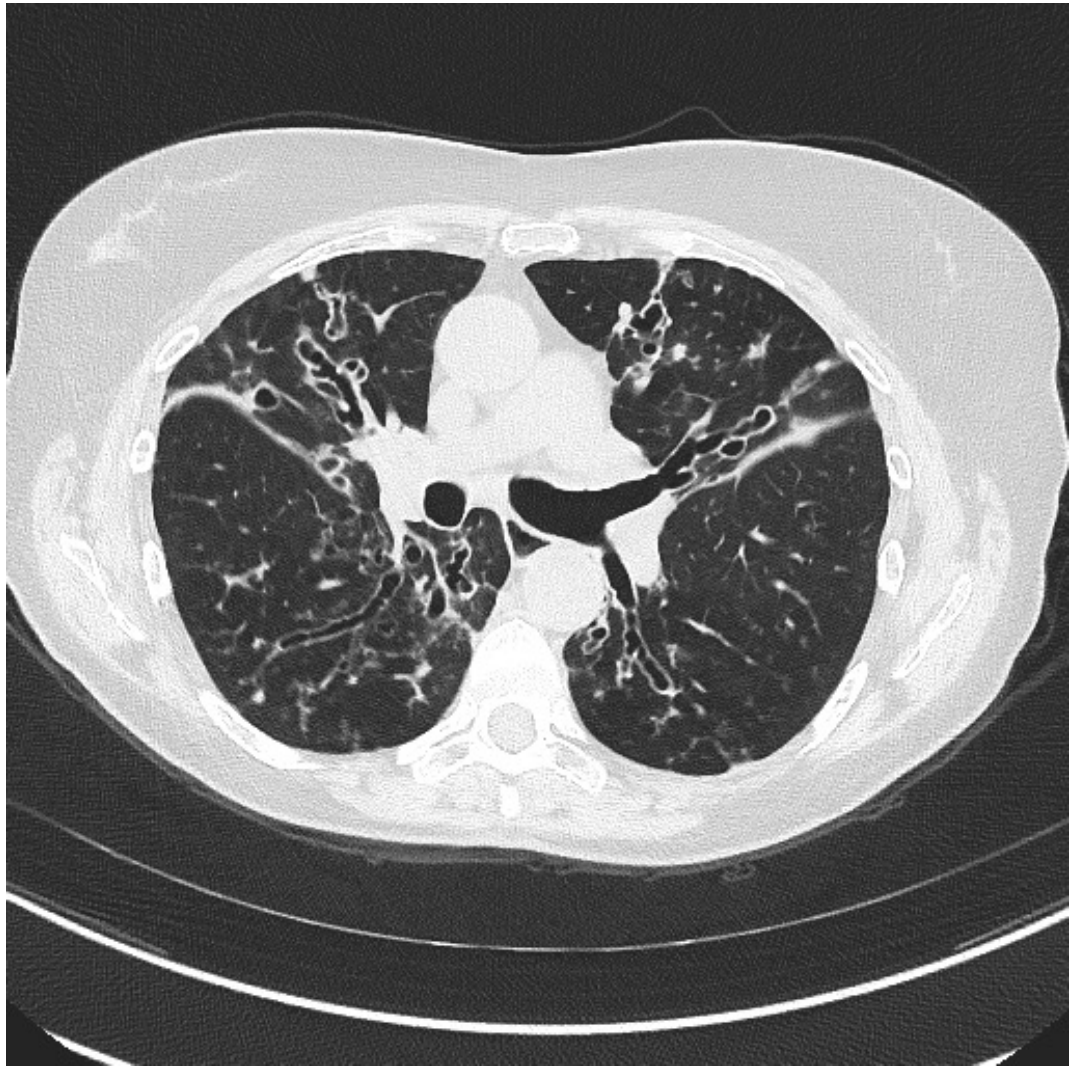
- Started on three times weekly therapy (azithromycin, ethambutol, and rifampin)
- Placed on airway clearance but initially had difficulty following directions and needed close collaboration with Pulmonary Service
- Advised to keep the head-end of hospital bed raised to prevent aspiration
- Completed 12 months of treatment with negative cultures (total of 16 months of therapy)
- Continues to be monitored every 3 months with sputum AFB smears and cultures

Case 2–History and Treatment Initiation

- A 66-year-old female with history of osteoporosis was diagnosed with MAC after 3 years of chronic cough and fatigue
- She was started on azithromycin 500 mg, ethambutol 1,200 mg, and rifampin 600 mg three time weekly by a local pulmonologist and instructed on airway clearance techniques

- Unfortunately, she felt nauseated after taking azithromycin so she self discontinued and remained on 2 drug therapy without a macrolide

Case 2–CT Scan Prior to Initiation of Therapy



Case 2–Adherence and 2-Drug Therapy

- She took 2-drug therapy for approximately 8 weeks but noticed no improvement
- She was then referred to an NTM center for further evaluation

- Sputum: 2+ on smear and 3+ on agar

Susceptibility:

Clarithromycin MIC 8

Amikacin MIC 8

Minimum Inhibitory Concentration (MIC) Breakpoints (mg/L) of the Antimicrobial Agents

Antibiotic	Susceptible	Intermediate	Resistant
Clarithromycin	≤ 8	16	≥ 32
Ethambutol	≤ 2	4	≥ 8
Rifampin	≤ 0.5	1, 2, and 4	≥ 8
Amikacin (IV)	≤ 16	32	≥ 64
Amikacin (ALIS)	≤ 64		≥ 128
Ciprofloxacin	≤ 1	2	≥ 4
Moxifloxacin	≤ 1	2	≥ 4
Linezolid	≤ 8	16	≥ 32

Woods GL, et al. Performance standards for susceptibility testing of mycobacteria. CLSI document M62. 2018

Macrolides and Amikacin for MAC Disease

- Treatment success correlates with *in vitro* macrolide (clarithromycin or azithromycin) 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)

Moon SM, et al. *Antimicrob Agents Chemother.* 2016;60:6758-6765.
Griffith DE, et al. *Am J Respir Crit Care Med.* 2007;175:367-416.
Brown-Elliot BA, et al. *J Clin Microbiol*. 2013;51:3389-94.
Olivier KN, et al. *Am J Respir Crit Care Med.* 2017;195:814-823.

Case 2–Restarting Treatment

- Azithromycin was restarted but this time she was instructed to take the meds at night
- Ethambutol and rifampin were continued, all three times weekly
- She submitted monthly sputum cultures which remains culture positive for MAC despite 8 months of this regimen with adherence
- She still complains of nausea related to macrolide therapy but feels the regimen is tolerable

What is the next best step?

A. Add inhaled liposomal amikacin suspension
B. Stop all NTM meds
C. Change medications to daily
D. Stop rifampin
E. A and C

Adding ALIS Increased Culture Conversion

Microbiologically Refractory/Treatment Failure

Evidence based practice–CONVERT study–Amikacin Liposomal Inhalation Suspension (ALIS)

- Amikacin-susceptible MAC-PD and positive sputum despite ≥ 6 mo guidelines-based therapy (GBT) randomized (2:1) to ALIS+GBT or GBT alone. ALIS 590 mg nebulized daily
- Primary endpoint: culture conversion (3 consecutive monthly sets (2-3 specimens each)) by month 6
- N = 224 ALIS + GBT vs 112 GBT alone, mean age 65, bronchiectasis in 63% and COPD in 14%
- Conversion: 65/224 **(29.0%) with ALIS + GBT** vs 10/112 **(8.9%) with GBT alone** (4.2 (2.1-8.6), $p < 0.001$)
- Respiratory adverse events (dysphonia, cough, and dyspnea) in 87% of ALIS + GBT and 50% of GBT participants. Adding ALIS to GBT in treatment-refractory MAC-PD achieved significantly greater culture conversion by month 6 than GBT alone.

Griffith et al. *Am J Respir Crit Care Med*. 2018;198:1559-1569.

Case 2–Adding ALIS

- Amikacin liposomal inhaled suspension (ALIS) was added to her three times weekly regimen
  - Changing her medication to daily was discussed but met with significant hesitancy given current side effects

- Two weeks after initiation, she called the nurse complaining of throat pain and cough
  - She was instructed to stop ALIS for 2 days and restart accompanied by drinking hot tea after inhalations

Case 2–Side Effects of Treatment

Returning to the office one week later, she:

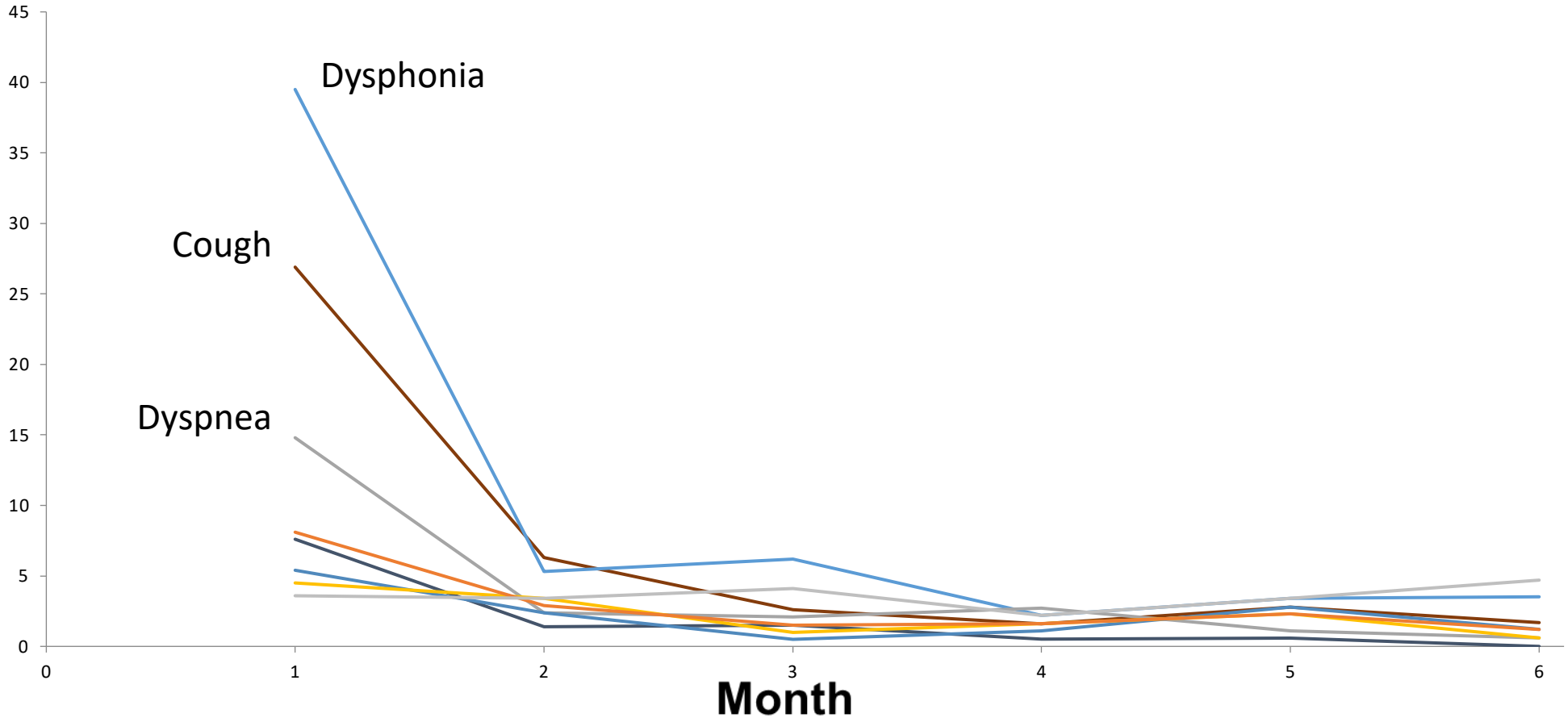
- Describes being adherent with the regimen but feels her voice has changed
- Does not feel she can sing at church and feels her voice is “tired” after long conversations
- Submits a sputum sample and would like to know if her voice is going to return to normal

Most Common Side Effects of ALIS

	ALIS + guideline based therapy N = 223	Guideline based therapy alone N = 112
	Patients, n (%)	Patients, n (%)
TEAEs occurring in ≥ 10% of patients in either arm		
Dysphonia	102 (45.7)	1 (0.9)
Cough	83 (37.2)	17 (15.2)
Dyspnea	48 (21.5)	10 (8.9)
Hemoptysis	39 (17.5)	15 (13.4)
Fatigue	36 (16.1)	8 (7.1)
Diarrhea	28 (12.6)	5 (4.5)
Nausea	25 (11.2)	4 (3.6)
Oropharyngeal pain	24 (10.8)	2 (1.8)

Griffith DE, et al. ATS 2018 May 18-23, San Diego, CA. A5915.

Convert Study: Adverse Events Over Time



Griffith DE, et al. ATS 2018 May 18-23, San Diego, CA. A5915

Case 2–Conversion, Continuing Therapy, and Follow-up

- She continued on her regimen and converted her sputum to negative after 4 months of ALIS therapy
- She then continued on her regimen for 12 months of negative cultures and therapy was stopped

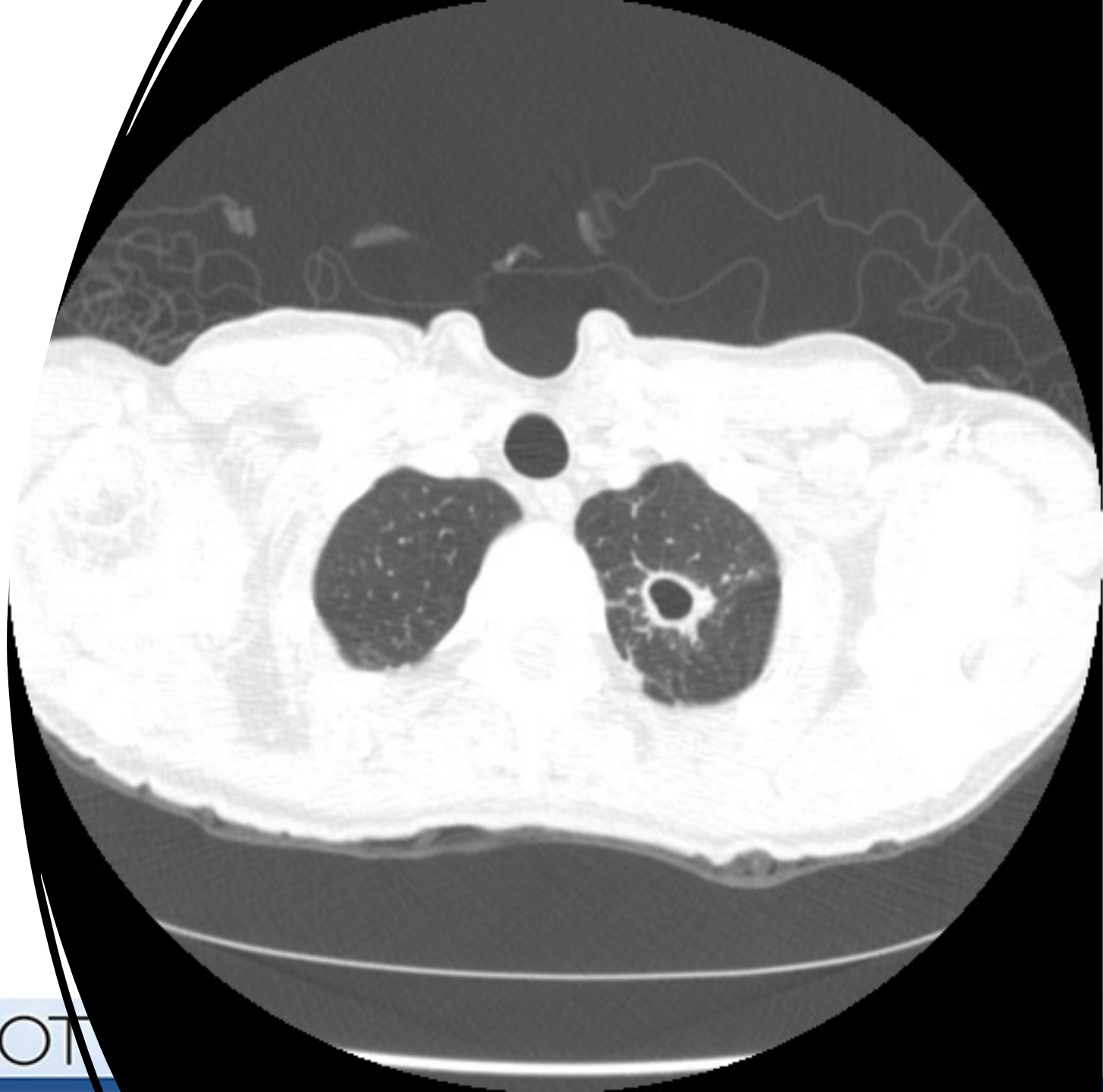
- She remained on airway clearance and follows up with her pulmonologist every 4-6 months
  - She submits sputum samples intermittently and has had 48 months of negative cultures for MAC

Case 3-History

- A 45-year-old female was referred to your clinic because of acute hemoptysis over the weekend
- She was seen at an urgent care center and given amoxicillin/clavulanate for an abnormal chest x-ray
- She describes a frequent cough over the past 5 years but is able to run 1 mile per day
- A CT scan was ordered

Case 3–CT Scan on Referral

- CT imaging revealing left upper lob cavitary disease
- No signs of bronchiectasis or other pulmonary findings noted



Case 3–Additional History AFB Results

- She has no significant past medical history
- She had been to Tibet on a missionary trip 2 years prior and concern for TB prompted health department involvement

- Her AFB sputum was reported as *Mycobacterium avium* complex (MAC) on 3 samples and she was referred to your center

Case 3–Susceptibility Testing

MAC

- Smear 4+
- 7H11 agar–4+
- Broth - + for AFB

Drug	MIC (mcg/mL)	Interpretation
Amikacin	8	S
Clarithromycin	8	S
Linezolid	> 64	R

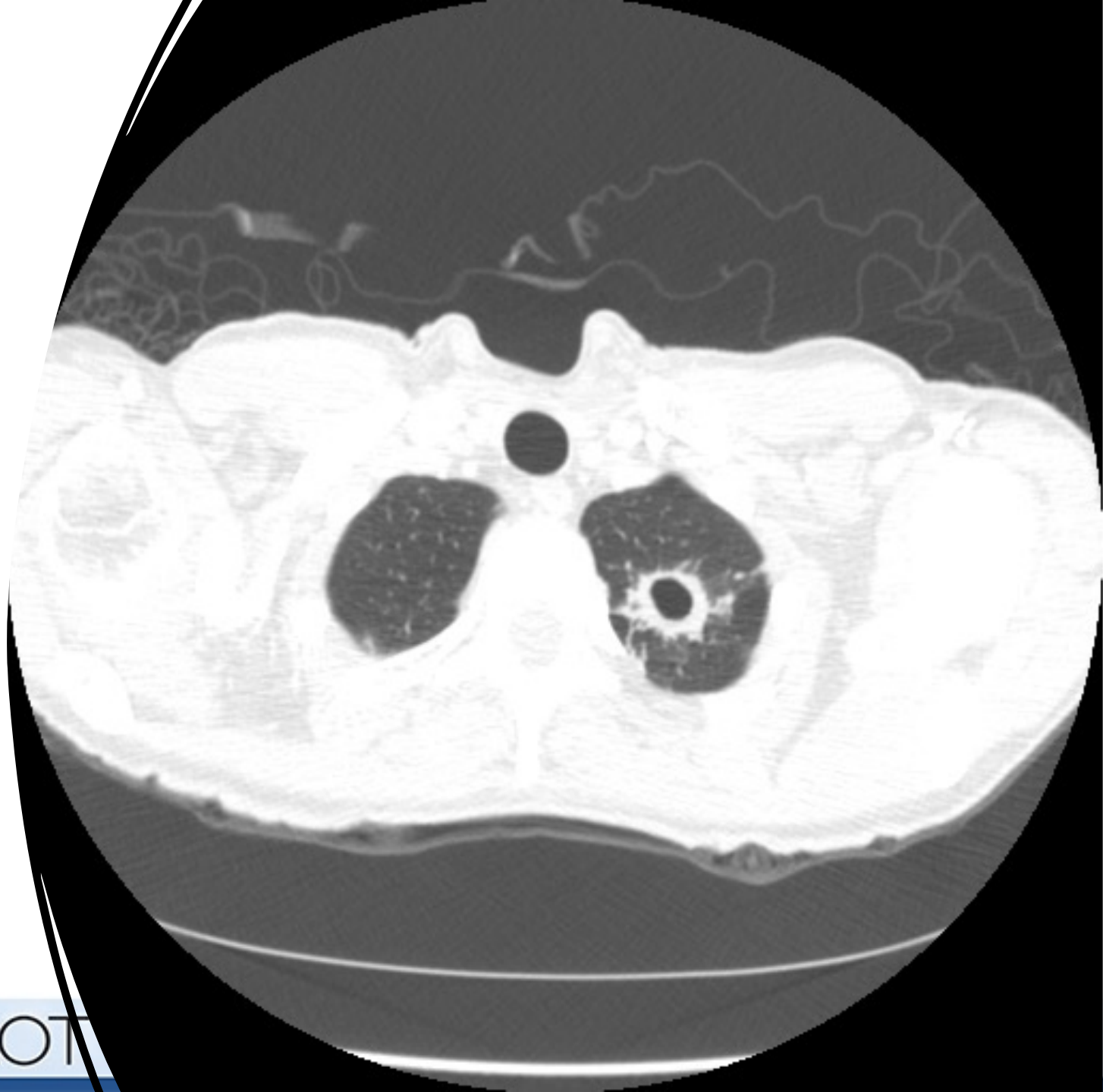
Case 3–Treatment Initiation

- She was placed on daily medications of azithromycin 250 mg, ethambutol 800 mg and rifampin 600 mg daily
- In addition, she underwent PICC line placement and IV amikacin 15 mg/kg was started three times weekly. Side effects were discussed
- Monthly sputums were ordered

4 Months Later…

- Despite 4 months of aggressive IV therapy and daily oral medications, sputums remained smear positive for MAC

- Repeat imaging: Persistent cavitary lesion with thickening of cavitary wall



What is the best next step?

A. Continue current regimen without changes for 12 months of therapy
B. Change IV amikacin to inhaled liposomal amikacin and continue oral meds
C. Continue current regimen and refer to a specialized surgery center
D. Stop IV amikacin, continue oral regimen, and referral to surgery

Surgical Considerations if…

- Disease is localized
- Drugs fail to convert the sputum cultures to negative
- Patients do not tolerate medical therapy
- Diagnosis is macrolide-resistant MAC pulmonary disease

* Low mortality rates at experienced centers

Mitchell JD, et al. *Ann Thorac Surg*. 2008;85(6):1887-1893.
Yu JA, et al. *Eur J Cardiothorac Surg*. 2011;40(3):671-675.

Treatment Considerations in Cavitary Disease

- Take cavitary disease seriously
- Treatment outcomes are worse in cavitary disease; use of injectable aminoglycosides can increase culture conversion. Daily oral therapy is recommended over three times weekly.
- IV Amikacin (or Streptomycin) is given 15 to 25 mg/kg 3 times per week for 8-16 weeks in addition to oral medications
- Use with caution with patients with renal disease. Some experts consider use of inhaled liposomal amikacin in these cases.

Ito Y, et al. *Int J Tuberc Lung Dis*. 2012;16(3):408-414.
Hayashi M, et al.. *Am J Respir Crit Care Med*. 2012;185(5):575-583.
Kobashi Y, et al. *Respir Med*. 2007;101(1):130-138.

Employ a Patient Education/Multidisciplinary Approach to Support Adherence to Treatment Plan

1. Pulmonologists
2. Infectious disease specialists
3. Primary care
4. Respiratory therapists
5. Dieticians
6. Thoracic surgeons
7. Physical therapy
8. Laboratory