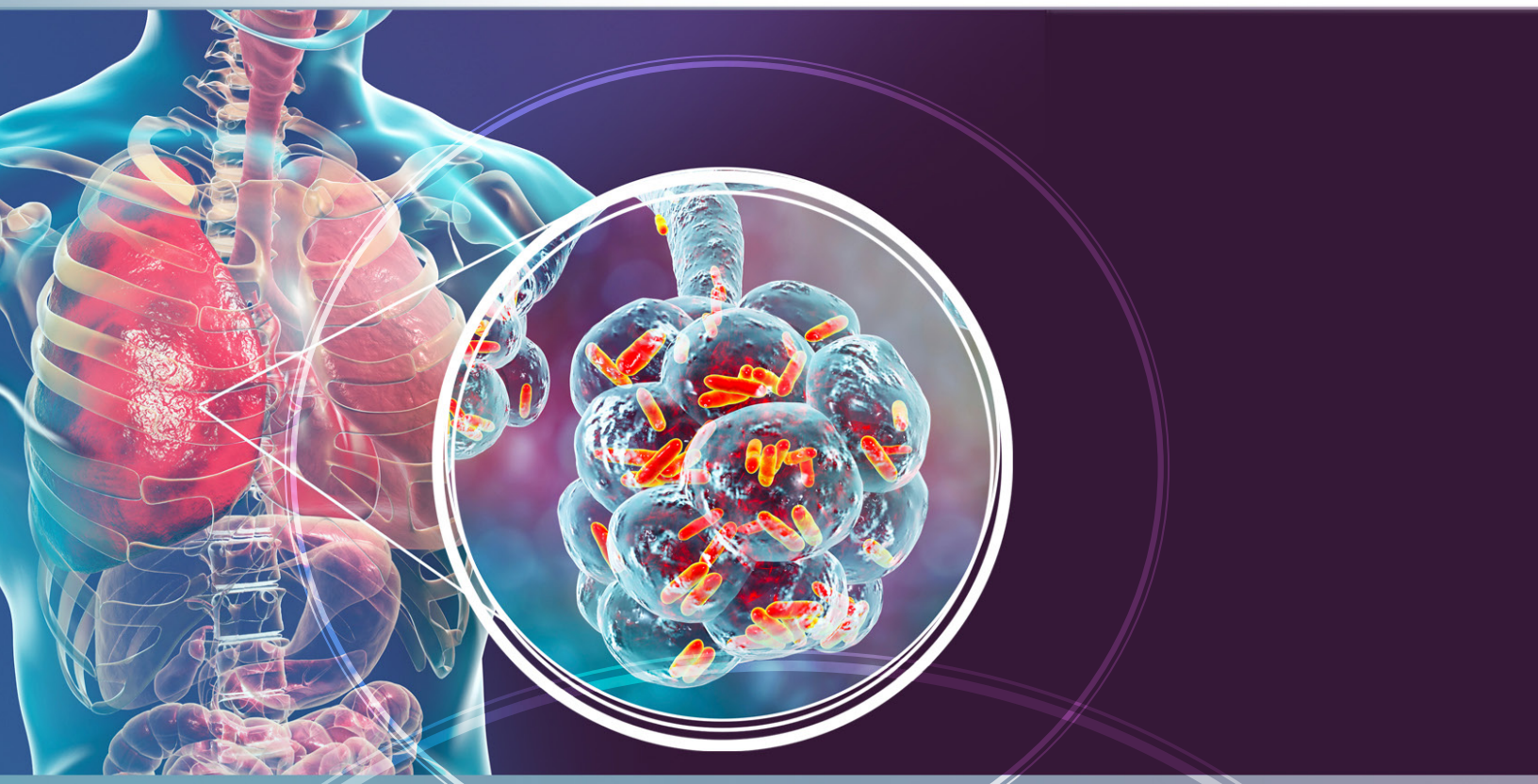
VIRTUAL WEBINAR

NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE (NTM-LD):

Individualizing Treatment Goals and Strategies – AN INNOVATIVE WHITEBOARD VIEW



Wednesday, October 20, 2021

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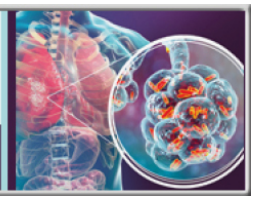

AGENDA

1) Nontuberculous Mycobacterial Lung Disease (NTM-LD) Overview
    a) NTM Species
        i) Epidemiology
        ii) Association of species with lung disease
        iii) Distinguishing colonization from active disease
    b) Historical, prospective and unmet therapeutic needs
    c) Patient characteristics
        i) Risk factors for NTM-LD
        ii) Pulmonary comorbidities and lung abnormalities associated with NTM-LD
        iii) NTM-LD in immunosuppressed patients
        iv) Genetic factors

2) Differential Diagnosis of NTM-LD
    a) Maintaining clinical suspicion for NTM-LD
    b) Clinical, radiographic, microbiological criteria
        i) Clinical manifestations of NTM-LD
        ii) Assessing patients with chronic cough for NTM-LD
        iii) Diagnosis of *Mycobacterium avium* complex lung disease
        iv) Interpretation of radiographic findings
    c) Drug susceptibility testing
        i) Culture utilization and interpretation

3) Treatment strategies for NTM-LD
    a) Individualization of treatment goals
        i) Developing treatment goals
        ii) Balancing risks and benefits of treatment vs no treatment
        iii) Treating underlying bronchiectasis
    b) Guidelines-based antibiotic regimens
        i) 2 and 3 agent combinations
        ii) Adjusting regimens in case of poor tolerability/toxicities/treatment failure
        iii) Toxicity monitoring considerations
        iv) Whiteboard Theme: Development of antibiotic tolerance and resistance in NTM
        v) Identifying and managing treatment-refractory disease
        vi) Liposomal formulations
    d) Patient-centered approach to therapy

4) Conclusions

5) Questions and Answers

Nontuberculous Mycobacterial Lung Disease (NTM-LD): Individualizing Treatment Goals and Strategies – An Innovative Whiteboard View

FACULTY

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PROGRAM OVERVIEW

This live virtual activity will explore the management of patients with nontuberculous mycobacterial lung disease (NTM-LD), including diagnosis, therapy selection, and strategies for assessing and treating patients with refractory disease.

TARGET AUDIENCE

This educational activity is designed to meet the educational needs of pulmonologists and infectious disease specialists involved in the management of patients with NTM-LD.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Utilize evidence-based clinical, radiographic, and microbiologic criteria in the evaluation and diagnosis of NTM-LD
- Develop individualized treatment goals centered on patient health status, comorbidities, and preferences
- Select therapy for patients with NTM-LD utilizing clinical guidelines and up-to-date evidence
- Employ evidence-based strategies for enhancing patient tolerance, adherence, and therapy completion in patients with NTM-LD

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Industry/Investigator Initiated Research	Beyond Air, BugWorks, Insmed, Paratek, Spero Therapeutics

Shannon Kasperbauer, MD is a speaker for AN2 Pharmaceuticals, Insmed and Paratek, and serves as a consultant for AN2 Pharmaceuticals, Insmed and Paratek.

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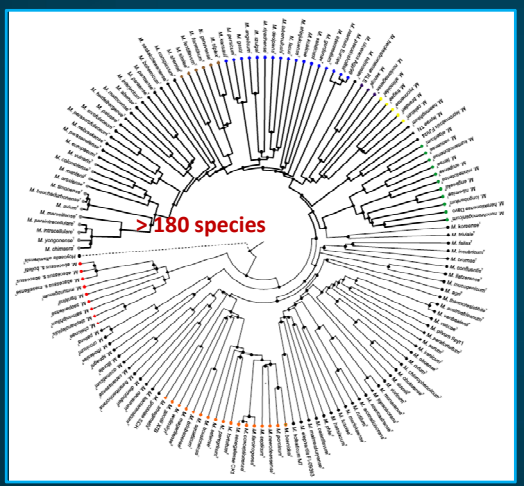
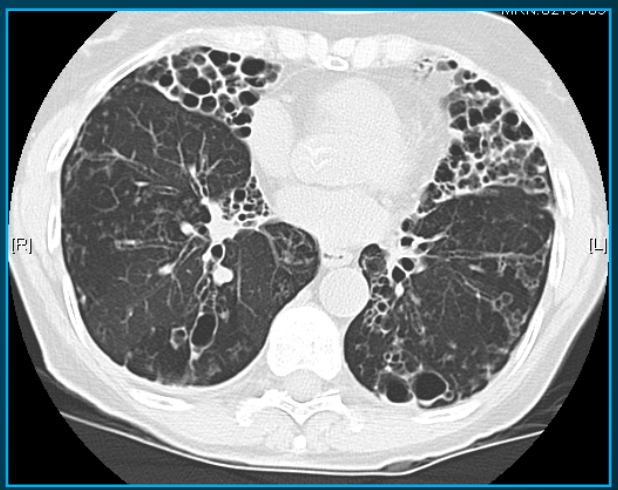
Learning Objectives

- Utilize evidence-based clinical, radiographic, and microbiologic criteria in the evaluation and diagnosis of NTM-LD
- Develop individualized treatment goals centered on patient health status, comorbidities, and preferences
- Select therapy for patients with NTM-LD using clinical guidelines and up-to-date evidence
- Employ evidence-based strategies for enhancing patient tolerance, adherence, and therapy completion in patients with NTM-LD

NTM-LD = nontuberculous mycobacterial lung disease.

What Is NTM Lung Disease?

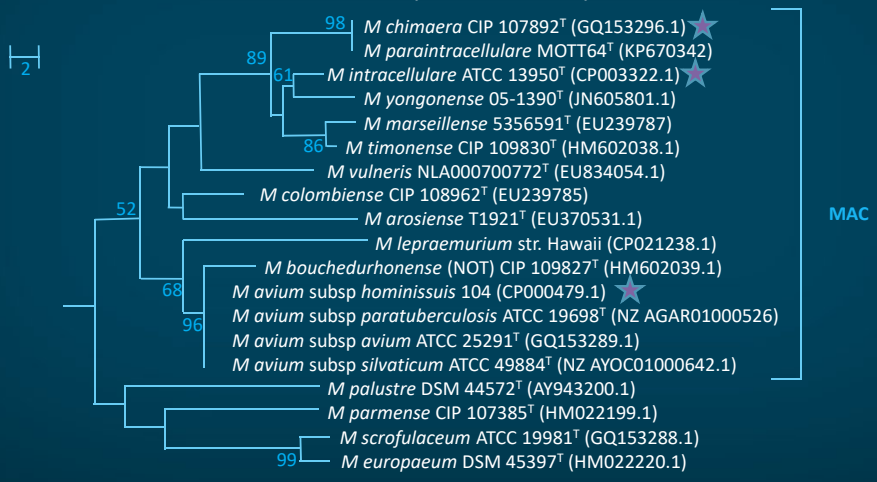




Tortoli E, et al. *Infect Genet Evol*. 2017;56:19-25.

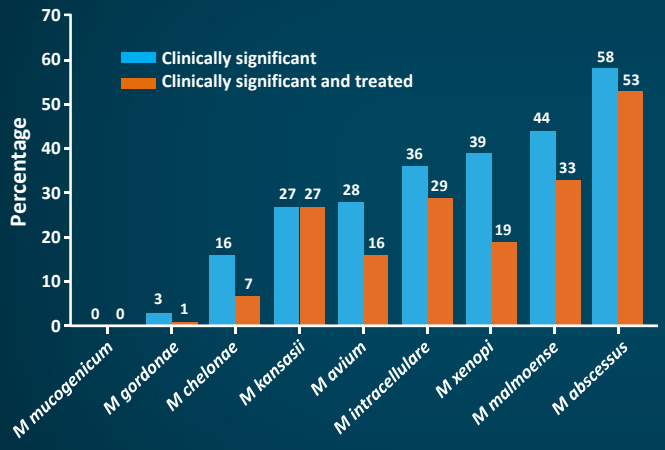
Mycobacterium avium Complex Is the Most Common NTM Pathogen

- 12 species of *Mycobacterium avium* complex (MAC)
  - *M avium*, *M intracellulare*, and *M chimaera* predominant species



Bar represents the number of nucleotide differences between species.
van Ingen J, et al. *Int J Syst Evol Microbiol*. 2018;68:3666-3677.

Colonization vs Active Disease?



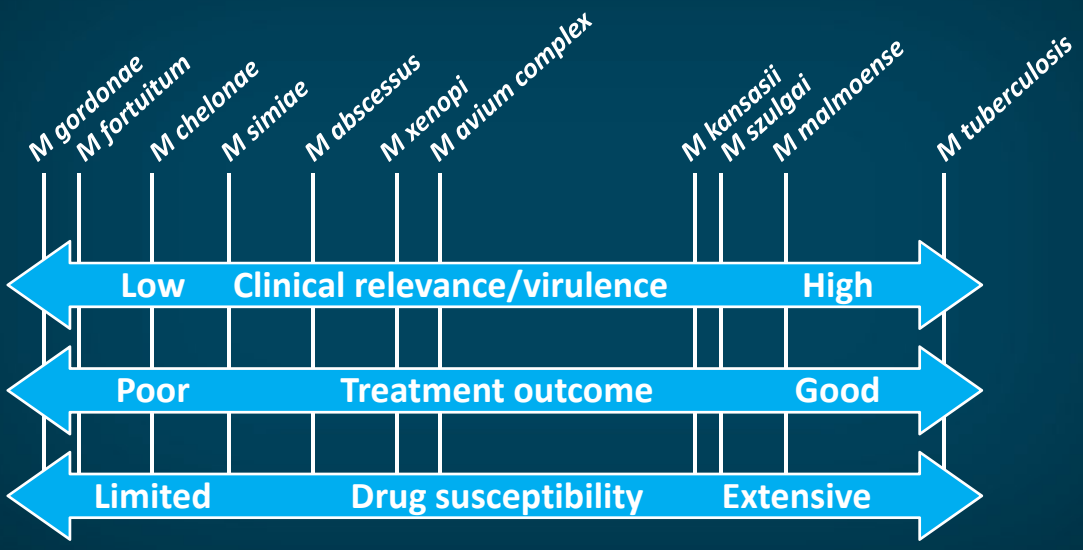
Patients meeting ATS/IDSA diagnosis criteria per total number of patients (%) by NTM species

Mycobacterial Species	Isolates, n (%)	Smear Positive, n	Clinical Episodes, n	Smear Positive by Clinical Episode, %
Intracellulare	267 (31.30)	8	124	33.33
Avium	181 (21.22)	5	75	6.67
Gordonae	130 (15.24)	1	109	0.92
Abscessus	72 (8.44)	12	19	63.16
Chelonae	72 (8.44)	8	45	17.78
Xenopi	67 (7.85)	4	36	11.11
Malmoense	40 (4.69)	3	18	16.67
Kansasii	16 (1.88)	1	11	9.09
Mucogenicum	8 (0.94)	0	7	0.00

853 isolates from 386 patients over 7 years in the United Kingdom

ATS = American Thoracic Society; IDSA = Infectious Diseases Society of America.
Schiff HF, et al. *Sci Rep*. 2019;9:1730.

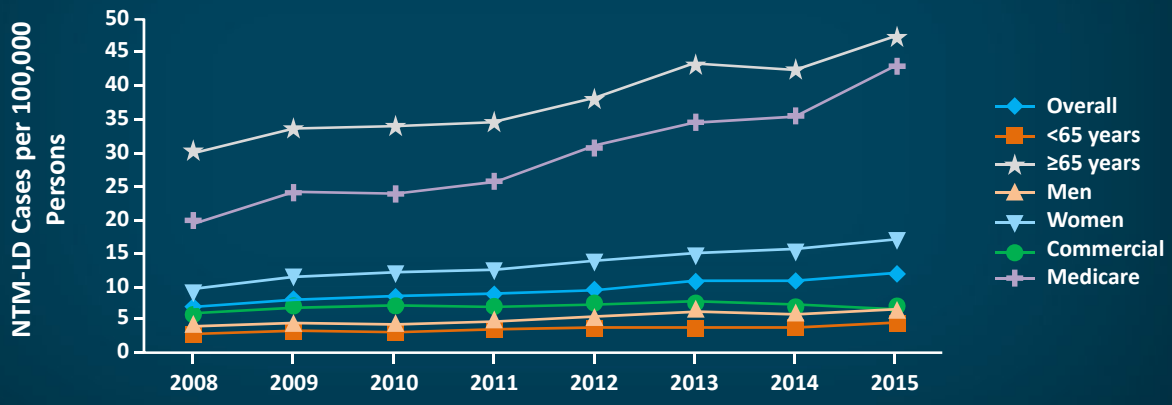
Colonization or Active Disease?



van Ingen J, et al. *Infect Genet Evol*. 2012;12:832-837.

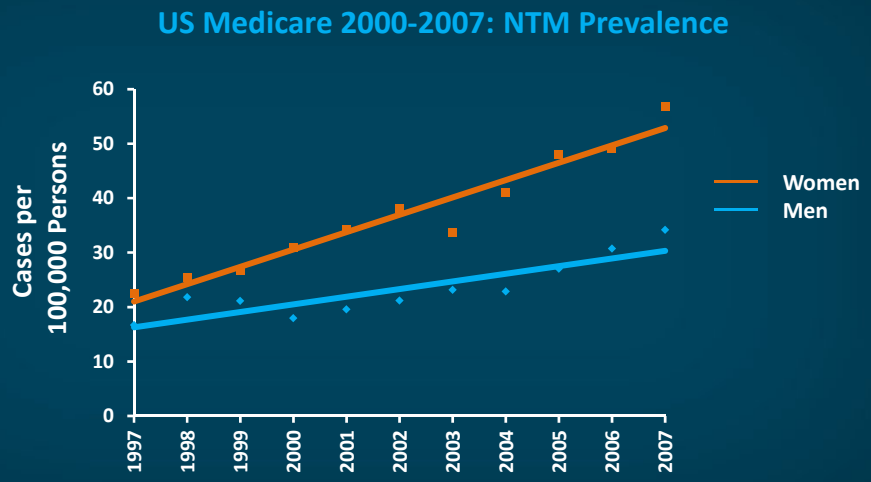
Older Individuals Are at Greater Risk

National Managed Care Claims Database –
27 million people annually
Prevalence (per 100,000)



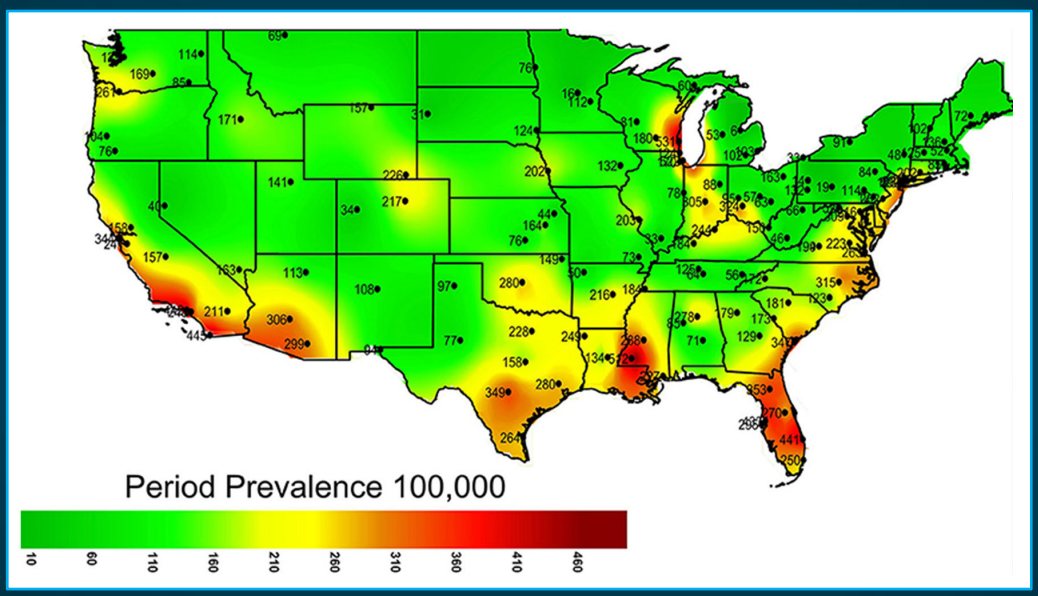
Winthrop KL, et al. *Ann Am Thorac Soc*. 2020;17:178-185.

Women Are Affected More Often Than Men



Adapted from Adjemian J, et al. *Am J Respir Crit Care Med*. 2012;185:881-886.

Higher Prevalence in Coastal Regions



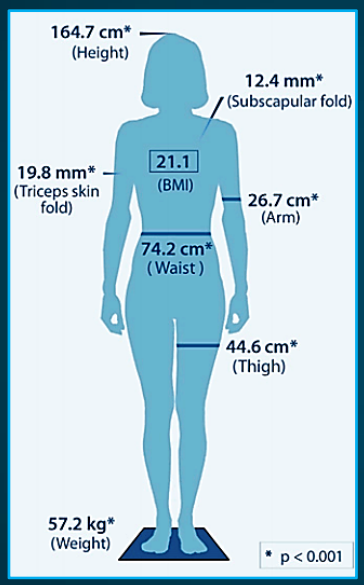
Pyarali FF et al. *Front Med (Lausanne)*. 2018;5:311.

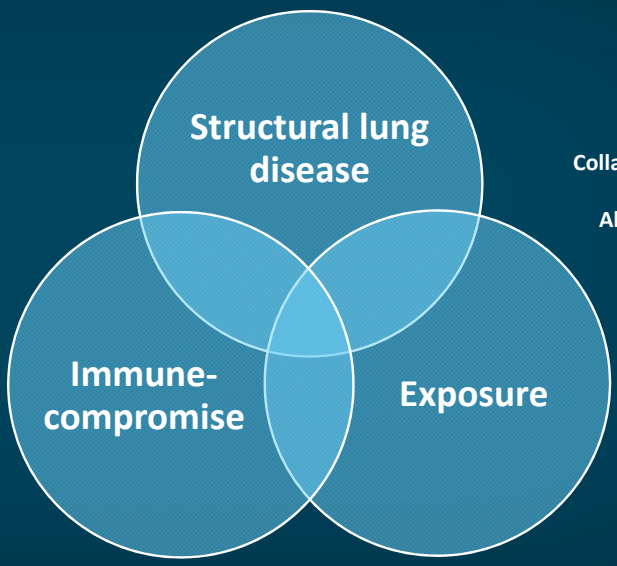
Unmet Needs

- Only 17% of patients with bronchiectasis are screened with NTM cultures[1]
- The average duration of symptoms prior to diagnosis of NTM-LD is 2 years[2]
- Once diagnosed, only 13% to 30% of individuals are treated with guideline-based therapy[3-5]

1. Finch S, et al. *Thorax.* 2019;74:A238-A239. 2. Ahmed I, et al. *Int J Infect Dis.* 2020;92:S46-S50. 3. Adjemian J, et al. *Ann Am Thorac Soc.* 2014;11:9-16. 4. Kim H, et al. *Medicine (Baltimore).* 2019;98:e17869. 5. Izumi K, et al. *ERJ Open Res.* 2020;6:00097-2019.

Patient Characteristics



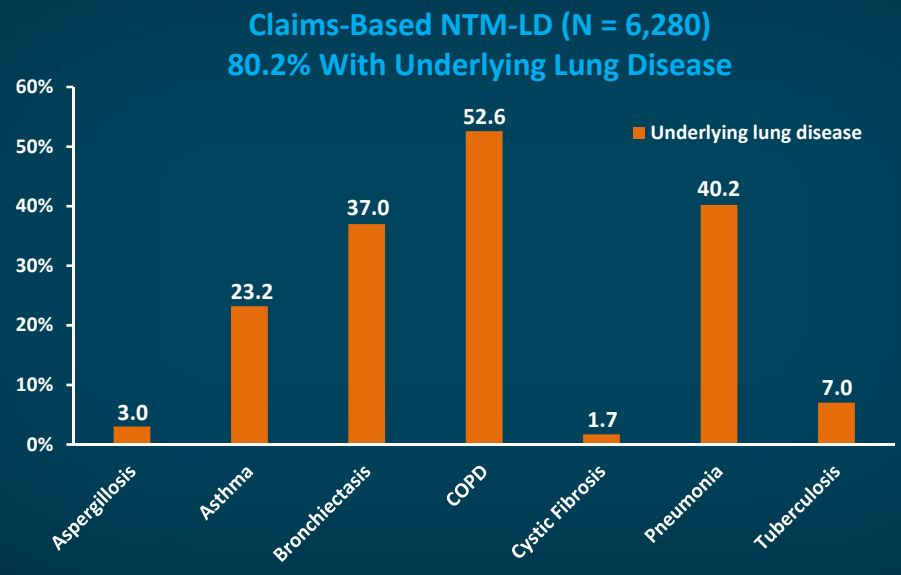


CF/CFTR anomalies
PCD
AAT anomalies
COPD
Asthma
Pneumoconiosis
Collagen vascular disease
Bronchiectasis
Alveolar proteinosis

AAT = alpha-1 antitrypsin; BMI = body mass index; CF = cystic fibrosis; CFTR = CF transmembrane conductance regulator; COPD = chronic obstructive pulmonary disease; PCD = primary ciliary dyskinesia.

Kim RD, et al. *Am J Respir Crit Care Med.* 2008;178:1066-1074.

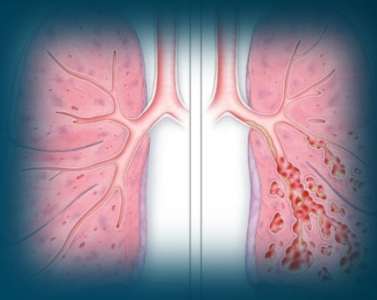
Underlying Lung Disease Is Common



Winthrop KL, et al. *Ann Am Thorac Soc.* 2020;17:178-185.

Risk Factors for NTM-LD

- NTM-LD OR for patients with COPD was[1]
  - 7.6 for those with no ICS use
  - 19.6 for those who had ever used ICSs
  - 29.1 for those with current ICS use
- Medicare recipients have high rates of NTM-LD: 112 patients in 100,000[2]
- The average prevalence rate for NTM infection in veterans with COPD is 148.9 patients in 100,000[3]
- In patients with CF the rate of NTM isolation is 12%[4]



ICS = inhaled corticosteroid; OR = odds ratio.

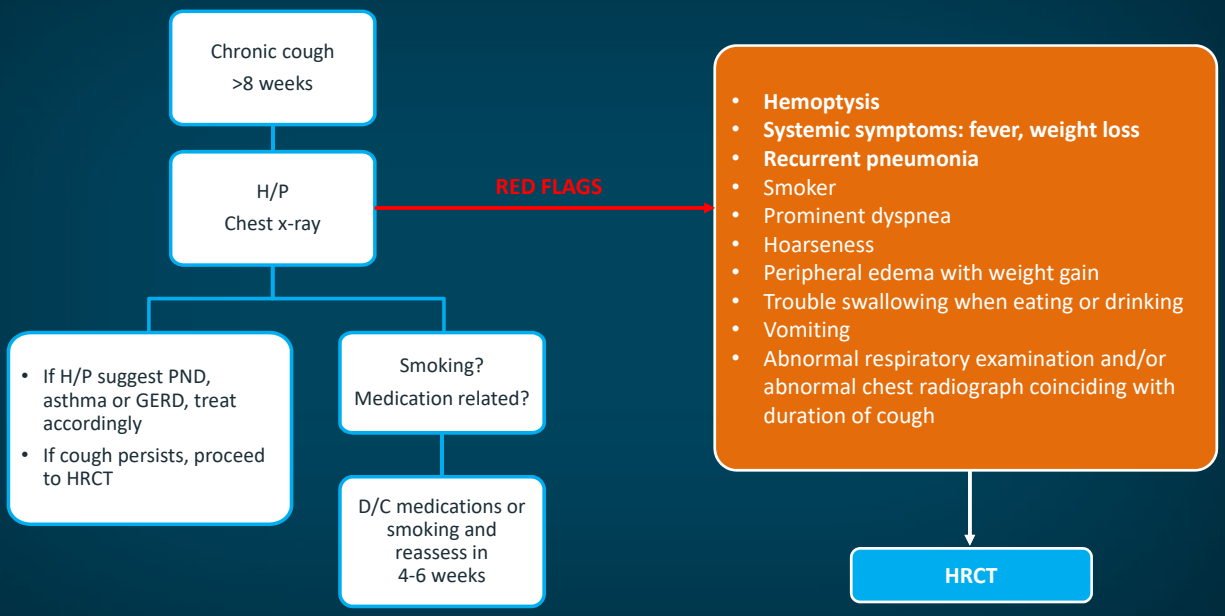
1. Andrejak C, et al. *Thorax.* 2013;68:256-262. 2. Adjemian J, et al. *Am J Respir Crit Care Med.* 2012;185:881-886.
3. Pyarali FF et al. *Front Med (Lausanne).* 2018;5:311. 4. Salsgiver EL, et al. *Chest.* 2016;149:390-400. 5. Barker AF. *N Engl J Med.* 2002;346:1383-1393.

Case of Chronic Cough

- 65-year-old woman from Colorado
- Chronic cough of 2 years, productive
- Weight loss
- Frequent “bronchitis”
- Past medical history: GERD
- Current medications: omeprazole
- Social history: lifelong nonsmoker

GERD = gastroesophageal reflux disease.

Patient Assessment



D/C = discontinue; H/P = history and physical; HRCT = high-resolution CT; PND = postnasal drip.
Irwin RS, et al. *Chest.* 2018;153:196-209.

Case Study: 65-Year-Old Woman With a Chronic Cough

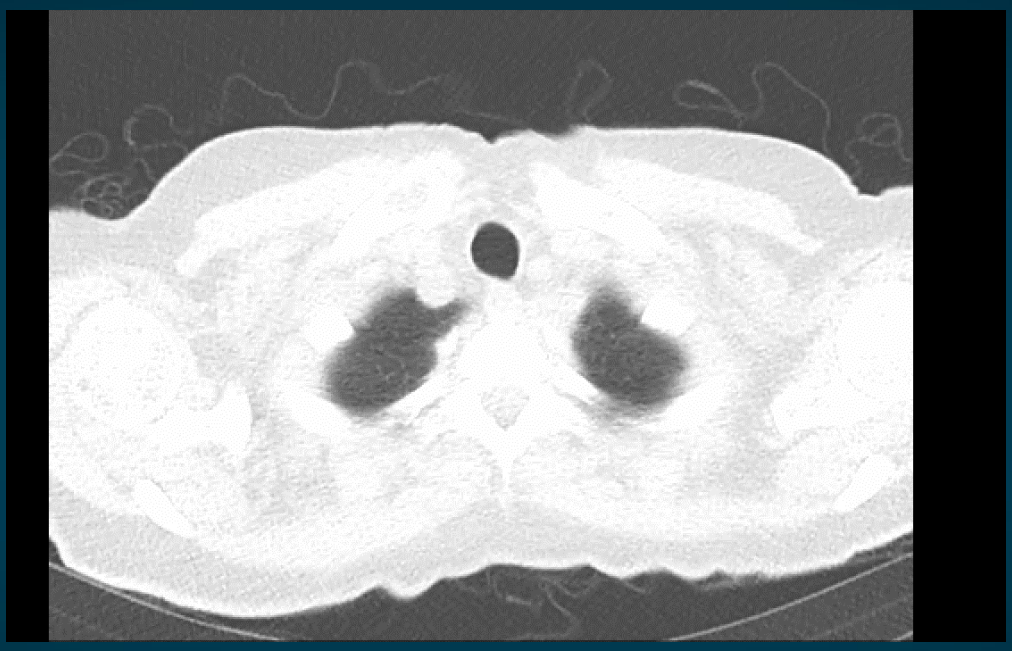
- 65-year-old woman from Colorado
- Chronic cough of 2 years, productive
- Weight loss
- Frequent “bronchitis”

- Physical examination: BMI, 17.5
  - Otherwise unremarkable

- Laboratory: CRP, 0.75 (<0.40)

- Microbiology: 3/3 sputum smear –
  - Culture + *M intracellulare*

CRP = C-reactive protein.



Diagnostic Steps

Only 17% of patients in EMBARC tested for NTM[1]…

Recognize chronic symptoms

Order HRCT chest

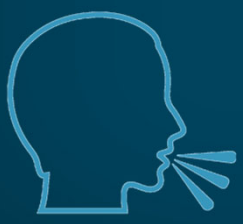
Obtain AFB cultures

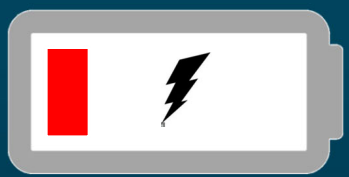
AFB = acid-fast bacilli.

1. Finch S, et al. *Thorax.* 2019;74:A238-A239.

Clinical Manifestations of NTM-LD

Median time from symptom onset to diagnosis of NTM-LD is 2 years





Symptom	Frequency (n = 63)
Fatigue	52 (83%)
Cough	49 (78%)
Phlegm	42 (67%)
Shortness of breath	41 (65%)
Night sweats	34 (54%)
Fever	28 (44%)
Hemoptysis	18 (29%)
Weight loss	3.7 ± 5.2 kg

Kim RD, et al. *Am J Respir Crit Care Med*. 2008;178:1066-1074. Ahmed I, et al. *Int J Infect Dis.* 2020;92:S46-S50.

Diagnosis of MAC-PD

Clinical	Pulmonary or systemic symptoms	Both required
Radiological	Nodular or cavitary opacities on chest radiograph or HRCT that show bronchiectasis with multiple small nodules	
Appropriate exclusion of other diagnoses		
Microbiological	1. Positive cultures from **≥2** separate sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **OR** 2. Positive cultures from **at least one** bronchial wash or lavage **OR** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and **≥1** sputum or bronchial washings that are culture positive for NTM	

- Culture to the species level is required
- Multiple specimens: 3 over ≥1 week, preferably over weeks
- Pursue sputum induction if patient is unable to expectorate

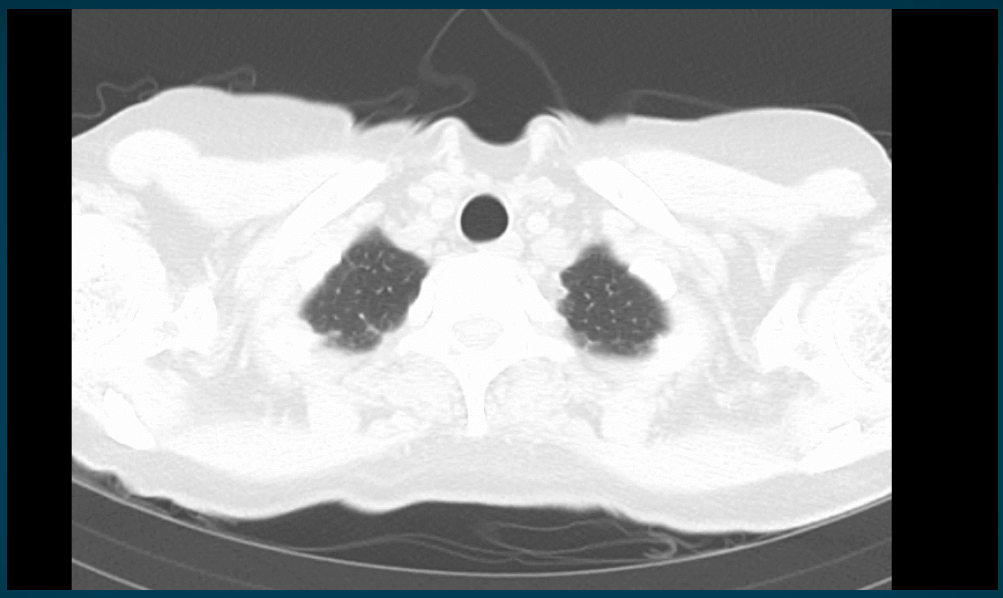
MAC-PD = MAC pulmonary disease.

Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

Interpretation of Radiographic Findings

- Bronchiectatic-nodular phenotype
- Lady Windermere: anterior lobes
- Lower lobe disease suggests:
  - GERD
  - Oropharyngeal dysphagia
  - Chronic sinusitis
  - Humoral immunodeficiency
  - Inflammatory bowel disease
  - PCD
- Upper lobe disease suggests:
  - CF
  - Allergic bronchopulmonary aspergillosis
  - Sarcoidosis

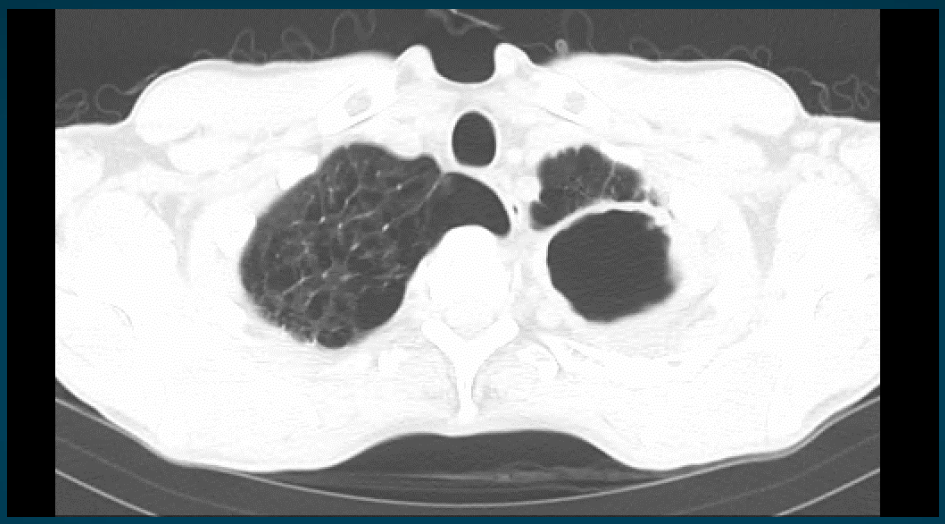
Koh, WJ et al. *Eur Respir J.* 2017;50:1602503. Hwang JA, et al. *Eur Respir J.* 2017;49:1600537.



Interpretation of Radiographic Findings

- Cavitary phenotype
- Fibrocavitary
  - Typically upper lobe
  - Underlying emphysema
  - Associated pleural thickening
- Cavitary nodular bronchiectatic
  - No lobar predominance

Koh, EJ et al. *Eur Respir J.* 2017;50:1602503. Hwang JA, et al. *Eur Respir J.* 2017;49:1600537.



Specimen Collection

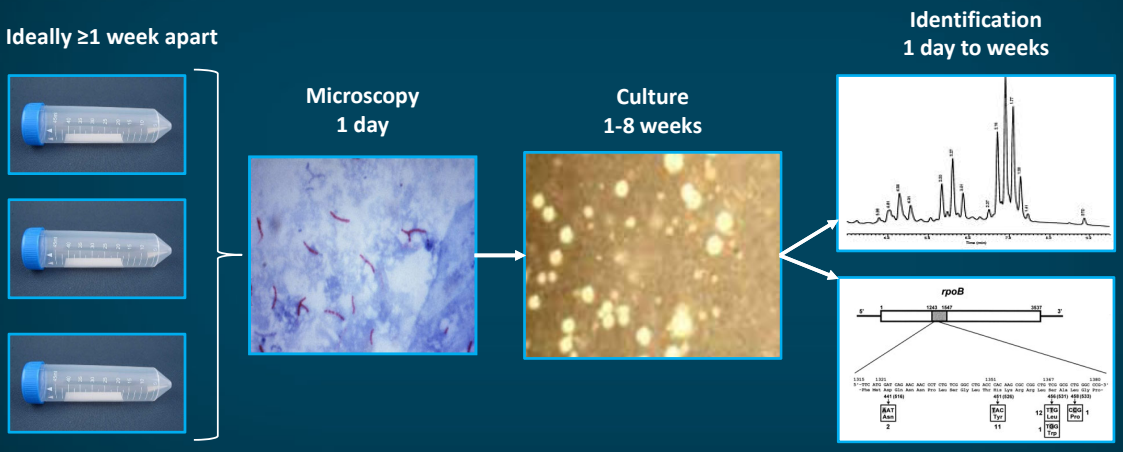
Bronchoscopy specimens

- Not as good as you think
  - Lidocaine is bacteriostatic
  - Specimen is dilute
  - Sampling error
  - Unable to determine bacterial load
  - Risks
  - Costs

Sputum

- Better than you think
  - Multiple specimens: 3 over ≥1 week, preferably over weeks
  - Sputum AFB smear positivity and number of cultures are associated with progression of NTM disease
  - Similar culture yield as bronchoscopy in tuberculosis and NTM
  - Induction with hypertonic saline is easy! Patients can do it at home

Culture and Identification



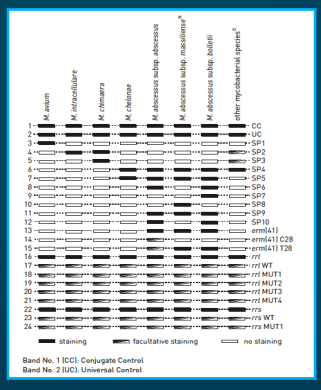
In MAC-PD, Guidelines Recommend Susceptibility-Based Treatment for Macrolides and Amikacin Over Empiric Therapy

Phenotypic Testing (weeks)

Antimicrobial Agent	MIC, µg/mL		
	S	I	R
Clarithromycin	≤8	16	≥32
Amikacin (IV)	≤16	32	≥64
Amikacin (liposomal inhaled)	≤64	–	≥128

CLSI. M62 Performance Standards for Susceptibility Testing, 2018

Genotypic Testing (hours/days)



rrl mutations (macrolide)

Sensitivity: 96.3%
Specificity: 100%

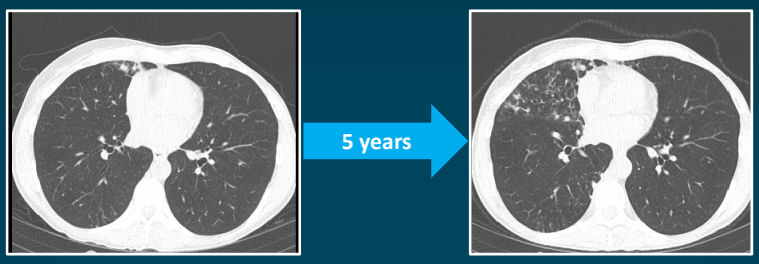
rrs mutations (aminoglycoside)

Sensitivity: 50%
Specificity: 100%

I = intermediate; IV = intravenous; MIC = minimum inhibitory concentration; R = resistant; S = susceptible.

Huh HJ, et al. *J Clin Micro.* 2019;57:e00516-e00519. Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

Why Is It Important to Diagnose and Treat NTM-LD?



NTM-LD

- Worsens underlying structural lung disease
- Impairs quality of life
- Increases mortality
- Increases healthcare resource utilization

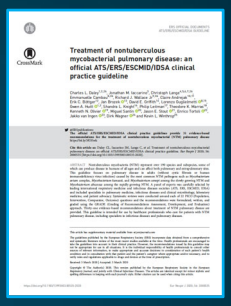
Mehta M, Marras TK. *Respir Med* 2011;105:1718-1725. Huang CT, et al. *Int J Tuberc Lung Dis.* 2012;16:539-545. Marras TK, et al. *J Manag Care Spec Pharm.* 2018;24:964-974. Marras TK, et al. *Respir Med.* 2018;145:80-88.

Treatment Strategies for NTM-LD

Dr. Charles L. Daley

NTM Treatment Guideline

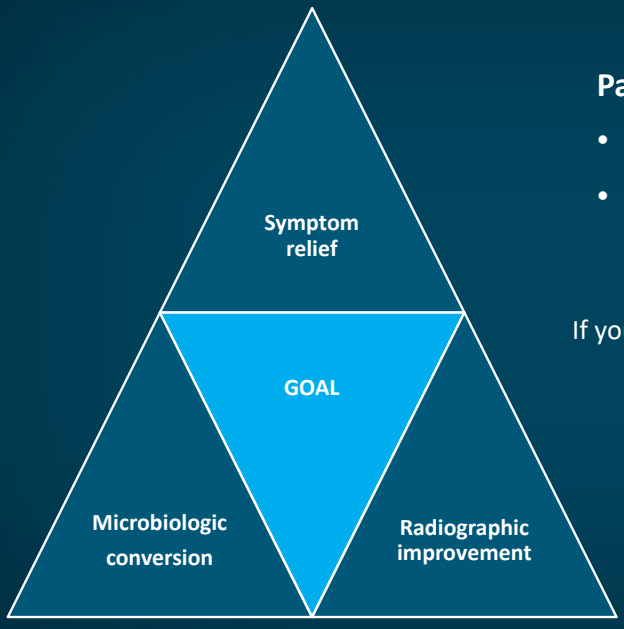
- Expert panel
  - 17 expert members
  - 2 methodologists
  - 1 medical librarian
  - 1 patient advocate
- Scope of guidelines
  - Pulmonary disease in adults (without HIV or CF)
  - *M avium* complex, *M kansasii*, *M xenopi*, *M abscessus*
- GRADE methodology
- 22 PICO (population, intervention, comparators, outcomes) questions
- 31 recommendations (7 MAC recommendations)
  - Strong (4): "recommend"
  - Conditional (28): "suggest"


Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline


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

Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

Treatment Goals



Patient's Perspective

- 57-question survey: NTMir
- 465 US patients with NTM

If your treatment could change 1 thing about your NTM lung infection, what would that be?

1. **Culture conversion**
2. **Less coughing**
3. **Less fatigue**

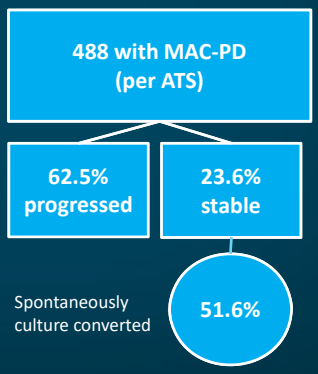
NTMir = NTM Info & Research.
NTM patient survey March 2019. Courtesy of Amy Leitman.

Initiate Treatment or "Watchful Waiting"?

Recommendation

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 AFB sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect)

- Host and organism factors are related to progression of disease
  - Some NTM species are more pathogenic than others
  - Immunocompromised patients at greater risk
- **Bacterial load** (ie, smear positive) and **radiographic extent of disease** (ie, cavitary) are predictors of progression
- Other predictors are older age, low BMI (<18.5), comorbidities, low albumin, anemia, and elevated inflammatory indices



Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535. Hwang JA, et al. *Eur Respir J.* 2017;49:1600537.

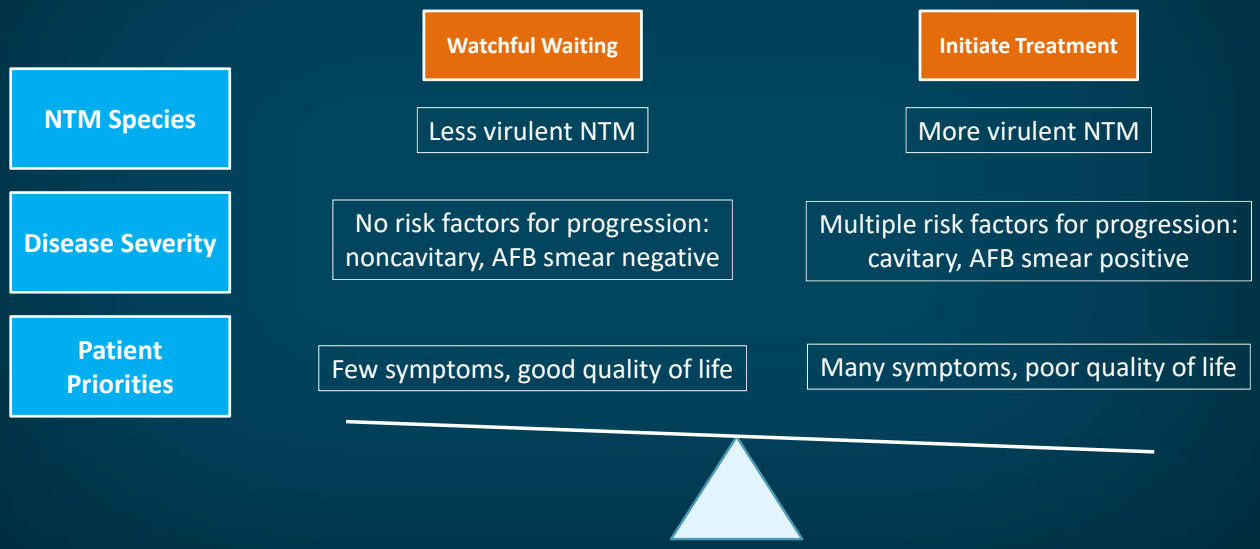
Who Should Be Treated? Risk Factors Associated With Progression

Host/Demographic Factors	Laboratory Factors	Radiographic Factors	Microbial Factors
• Male gender • Older age • Presence of comorbidities • Low BMI	• Elevated inflammatory indices (ESR, CRP) • Anemia • Hypoalbuminemia	• Fibrocavitary • Extent of disease	• Bacterial load • Species

ESR = erythrocyte sedimentation rate.

Hwang JA, et al. *Eur Respir J.* 2017;49:1600537. Kwon BS, et al. *Respir Med.* 2019;150:45-50. Moon SM, et al. *Respir Med.* 2019;151:1-7. Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

Decision to Treat



Daley CL, et al. *Clin Infect Dis.* 2020;71:905-913. Daley CL, et al. *Eur Respir J.* 2020;56:2000535.

Case Study: 65-Year-Old Woman With a Chronic Cough

- 65-year-old woman from Colorado
- Chronic cough of 2 years, productive
- Weight loss
- Frequent "bronchitis"

- Physical examination: BMI, 17.5
  - Otherwise unremarkable

- Microbiology: 3/3 sputum smear –
  - Culture + *M intracellulare*

Risk Factors for Progression
- "Older age"
- Low BMI
- Elevated CRP
- Comorbidities

Always Treat the Underlying Bronchiectasis

- Initiate airway clearance
- Evaluate and treat GERD
- Manage other comorbidities
  - CF, alpha-1 deficiency, common variable immunodeficiency, etc
- Improve nutrition
- Treat other concurrent infections (*Pseudomonas*)

Carro LM, Martínez-García MA. *Ther Adv Respir Dis*. 2019;13:1753466619866102.

Recommended Initial Treatment Regimens for MAC-PD

	No. of Drugs	Preferred Regimen*	Dosing Frequency
Nodular bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)†	Daily (IV aminoglycoside may be used 3 times weekly)

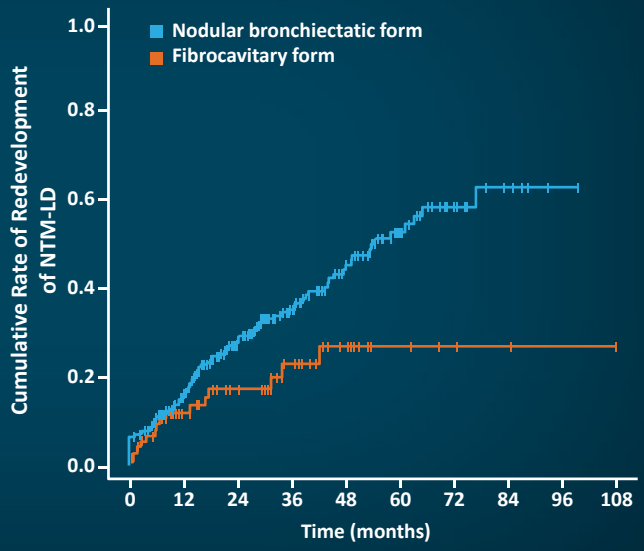
*Alternative drugs could include clofazimine, moxifloxacin, linezolid (tedizolid), and bedaquiline.

†Consider for cavitary, extensive nodular bronchiectatic, or macrolide-resistant disease.

Daley CL, et al. *Clin Infect Dis*. 2020;71:905-913. Daley CL, et al. *Eur Respir J*. 2020;56:2000535.

Treatment Outcomes for MAC

	Culture Conversion
Macrolide susceptible	
Noncavitary	80%
Cavitary	50%-80%
Macrolide resistant	
No surgery/aminoglycoside*	5%
Some surgery/aminoglycoside	15%
Surgery + prolonged aminoglycoside*	80%



*≥6 months parenteral aminoglycoside.

Griffith DE, et al. *Am J Respir Crit Care Med.* 2006;174:928-934. Wallace R, et al. *Chest.* 2014;146:276-282. Jeong BH, et al. *Am J Respir Crit Care Med.* 2015;191:96-103. Koh WJ, et al. *Eur Respir J.* 2017;50:1602503. Moon SM, et al. *Eur Respir J.* 2016;50:1602503. Morimoto K, et al. *Ann Am Thorac Soc.* 2016;13:1904-1911.

Monitoring Response to Therapy: What Improves?

- Retrospective cohort study of 217 patients with treatment-naive noncavitary MAC-PD at Samsung Medical Center in Seoul, South Korea
- Patients received 3-drug regimen (macrolide, ethambutol, rifampin)
- All patients received daily therapy before January 2011 and intermittent therapy after that date

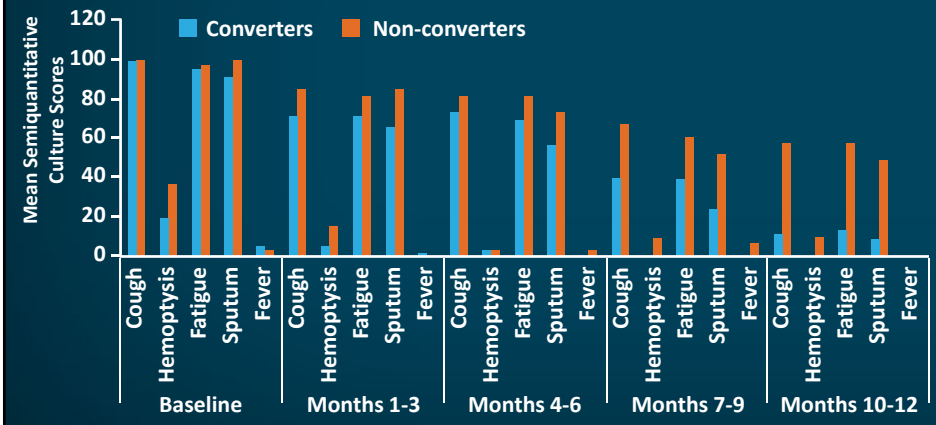
Treatment Outcome	Daily (n = 99)	Intermittent (n = 118)	*P*-value
Symptomatic improvement, n (%)	74 (75)	97 (82)	.181
Radiographic improvement, n (%)	67 (68)	86 (73)	.402
Culture conversion, n (%)	75 (76)	79 (67)	.154
Time to conversion, median (IQR), days	34 (27-68)	35 (28-85)	.149

IQR = interquartile range.

Jeong BH, et al. *Am J Respir Crit Care Med.* 2015;191:96-103.

Correlation of Change in Symptoms, Radiographs, and Semiquantitative Culture Results With Culture Conversion

- 180 patients treated with standard MAC therapy at University of Texas, Tyler
- Semiquantitative cultures were obtained throughout the course of therapy



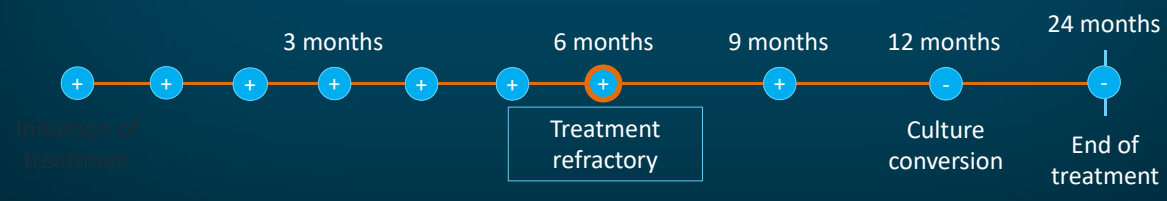
Early semiquantitative sputum agar plate culture results can be used to predict symptomatic and radiographic improvement as well as long-term sputum culture conversion to negative

Griffith DE, et al. *Am J Respir Crit Care Med.* 2015;192:754-760.

Monitoring Mycobacterial Culture Response to Therapy

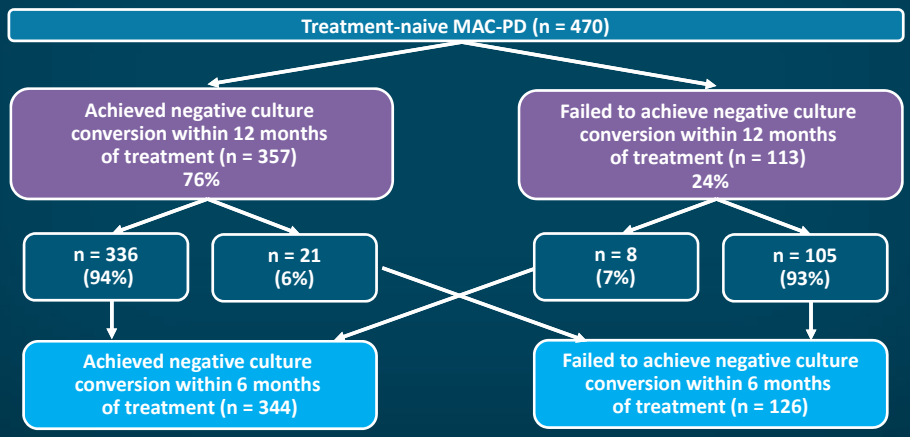
- Time of sputum culture conversion defines total duration of therapy

- Lack of sputum culture conversion defines "treatment refractory"



Culture Status at 6 and 12 Months in MAC-PD

470 patients with treatment-naive MAC-PD, Samsung, Seoul, South Korea



Moon SM, et al. *Eur Respir J.* 2019;53:1801636.

Development of antibiotic tolerance and resistance in NTM

https://youtu.be/ybaKmM0JZN0

Case Study: 65-Year-Old Woman With a Chronic Cough

- Patient is started on a 3-drug macrolide-containing regimen administered 3 times weekly given her noncavitary disease
  - Azithromycin 500 mg
  - Ethambutol 2,400 mg
  - Rifampin 600 mg
- She tolerated the medications well, her cough improved, and she gained a small amount of weight
- However, after 6 months, her cultures remained positive
- **What treatment options are available?**

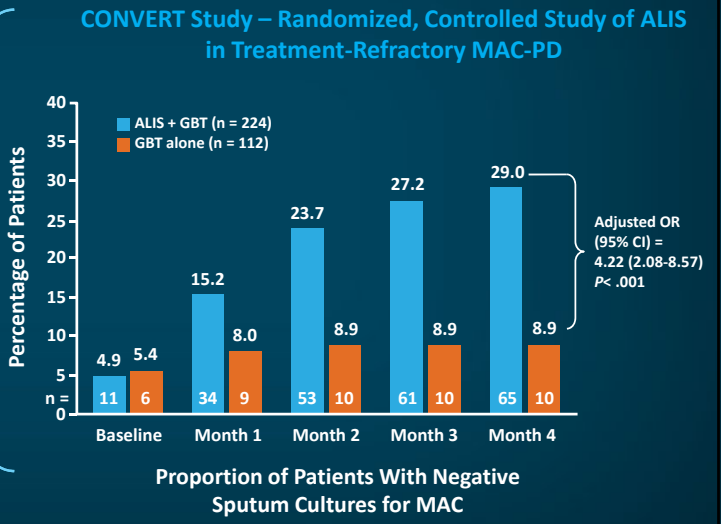
Treatment Refractory MAC-PD

Inhaled Amikacin

Recommendation

In patients with newly diagnosed MAC-PD, we suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension (ALIS) be used as part of the initial treatment regimen (conditional recommendation, very low certainty in estimates of effect)

In patients with MAC-PD who have failed therapy after ≥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)



GBT = guideline-based therapy.

Daley CL, et al. *Clin Infect Dis*. 2020;71:905-913. Daley CL, et al. *Eur Respir J*. 2020;56:2000535. Griffith D, et al. *Am J Respir Crit Care Med*. 2018;198:1559-1569.

Managing Adverse Drug Reactions

- Adverse drug reactions are very common during the treatment of MAC
- Adverse drug reactions can lead to:
  - Interruption in treatment, morbidity, and in some cases nonadherence and discontinuation of therapy
- Alterations in therapy may adversely impact treatment outcomes
- Strategies are needed to decrease drug-related toxicity and improve management of side effects and adherence to treatment

Adverse Drug Reactions in Patients Treated for Pulmonary MAC by Type

- Retrospective, study of 364 patients in Tokyo given ≥2 drugs (clarithromycin, rifampin, or ethambutol) for MAC-PD

	Hepatotoxicity	Leukocytopenia	Thrombocytopenia	Cutaneous Reactions	Ocular Toxicity
Prevalence, %	19.5	20.0	28.6	9.3	7.7
Time to onset, days	55	41	61.5	30	278
Duration, days	59	261	431	NA	NA
Discontinuation, %	2.8	1.4	1.0	11.8	96.2
			Usually due to rifampin		Due to ethambutol; improved in 52% within 5 months

Kamii Y, et al. *Int J Tuberc Lung Dis.* 2018;22:1505-1510.

Treatment of MAC Infection
Monitoring for Adverse Reactions

Macrolide	Ethambutol	Rifampin	Amikacin
• QT prolongation • GI side effects • Hearing loss	• Optic neuritis • Neuropathy	• Hematologic • GI intolerance • Malaise	• Renal • Vestibular • Ototoxicity

- CBC, liver function tests, and metabolic panel every 1-3 months
- Frequency depends on regimen, age, comorbidities, concurrent drugs, overlapping toxicities, and resources

Daley CL, et al. *Clin Infect Dis*. 2020;71:905-913. Daley CL, et al. *Eur Respir J*. 2020;56:2000535.

CONVERT Study of Amikacin Liposome Inhalation Suspension
Treatment Emergent AEs

AE	GBT + ALIS	GBT
Respiratory-related AEs		
Dysphonia	45.7%	0.9%
Cough	37.2%	15.2%
Dyspnea	21.5%	8.9%
Hemoptysis	17.5%	13.4%
Oropharyngeal pain	10.8%	1.8%
Audiological AEs		
Tinnitus	7.6%	0.9%
Dizziness	6.3%	2.7%
Hearing loss	4.5%	6.3%
Serious AEs	20.2%	17.9%
Discontinuation of ALIS	17.5%	–

Black Box Warning

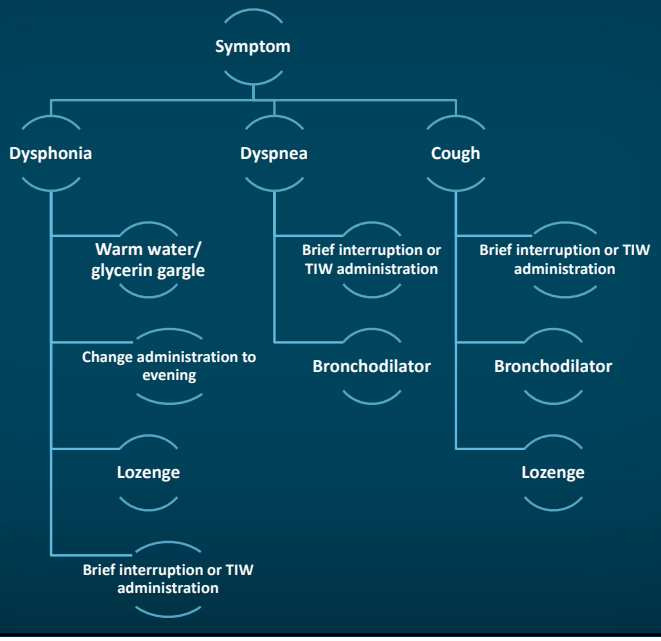
ALIS has been associated with an increased risk of respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbations of underlying pulmonary disease that have led to hospitalizations in some cases.

AE = adverse event.

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

Amikacin liposome inhalation suspension PI 2018 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207356s000lbl.pdf). Accessed May 4, 2021.

Amikacin Liposome Inhalation Solution
Management of AEs



TIW = 3 times weekly.

Swenson C, et al. *Open Forum Infect Dis*. 2020;7:ofaa079.

Patient-Centered Approach to Therapy

- Multidisciplinary approach to therapy
  - Importance of addressing comorbidities, GERD, nutrition, mental health issues, airway clearance, and pulmonary rehabilitation
- Review reasons for treatment and realistic expectations
  - Risk factors for progression, **goals of therapy**
- Review how treatment response will be assessed
  - Sputum cultures every 1-2 months
- Review side effects of medications, monitoring plans, and possible treatment interventions should side effects occur
  - Stopping offending drugs, drug "holidays", or alternative treatment options

NTM Future Treatments

Drug	Indication	Activity	Use
Antibiotics			
ALIS	MAC	MAC (new diagnosis)	Clinical trials
SPR720	None	MAC	Clinical trial
Bedaquiline	Multidrug-resistant tuberculosis	MAC, *M abscessus*	Off-label use
Clofazimine	Leprosy	All mycobacteria	Clinical trial Off-label use
Omadacycline	Bacterial infections	*M abscessus*	Clinical trial planned
Beta-lactams	Pseudomonas	*M abscessus*	Off-label use
Other agents			
Inhaled nitric oxide	ICU	All organisms	Clinical trial Off-label use
Inhaled gallium	None	NTM	Clinical trial
Bacteriophages	None	All organisms	Compassionate use

Key Points

- Laboratory diagnosis should include precise speciation and determination of *in vitro* susceptibility testing to at least macrolides and amikacin
- Diagnosis of NTM-related disease includes synthesis of clinical, radiographic, and microbiologic information
- For those who meet diagnostic criteria, initiation of therapy is preferred, especially for those with higher bacterial load and extensive radiographic disease
- MAC should be treated with a 3-drug macrolide-containing regimen for 12 months after culture conversion to negative
  - Nodular bronchiectatic disease can be treated 3x/week
  - Cavitary disease should be treated daily and parenteral aminoglycoside considered for first 2-3 months
- Treatment refractory MAC-PD should have ALIS added to guideline-based therapy

Thank You!

Q & A

Nontuberculous Mycobacterial Lung Disease (NTM-LD):
Individualizing Treatment Goals and Strategies

Resource	Address
Schiff HF, et al. **Clinical relevance of non-tuberculous mycobacteria isolated from respiratory specimens: seven year experience in a UK hospital.** *Sci Rep*. 2019;9:1730.	https://pubmed.ncbi.nlm.nih.gov/30741969/
Irwin RS, et al. **Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report.** *CHEST.* 2018;153:196-209.	https://pubmed.ncbi.nlm.nih.gov/29080708/
Ahmed I, et al. **Non-tuberculous mycobacterial infections-A neglected and emerging problem.** *Int J Infect Dis*. 2020;92S:S46-S50.	https://pubmed.ncbi.nlm.nih.gov/32114200/
Koh EJ, et al. **Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype.** *Eur Respir J*. 2017;50:1602503.	https://pubmed.ncbi.nlm.nih.gov/28954780/
Daley CL, et al. **Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline.** *Clin Infect Dis.* 2020;71:905-913.	https://pubmed.ncbi.nlm.nih.gov/32797222/
Hwang JA, et al. **Natural history of *Mycobacterium avium* complex lung disease in untreated patients with stable course.** *Eur Respir J*. 2017;49:1600537.	https://pubmed.ncbi.nlm.nih.gov/28275170/
Kwon BS, et al. **The natural history of non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease.** *Resp Med.* 2019;150:45-50.	https://pubmed.ncbi.nlm.nih.gov/30961950/
Moon SM, et al. **Long-term natural history of non-cavitary nodular bronchiectatic nontuberculous mycobacterial pulmonary disease.** *Resp Med.* 2019;151:1-7.	https://pubmed.ncbi.nlm.nih.gov/31047103/
Jeong BH, et al. **Intermittent antibiotic therapy for nodular bronchiectatic *Mycobacterium avium* complex lung disease.** *Am J Resp Crit Care Med.* 2015;191:96-103.	https://pubmed.ncbi.nlm.nih.gov/25393520/
Griffith DE, et al. **Semiquantitative Culture Analysis during Therapy for *Mycobacterium avium* Complex Lung Disease.** *Am J Respir Crit Care Med.* 2015;192:754-760.	https://pubmed.ncbi.nlm.nih.gov/26068042/
Moon SM, et al. **Unresolved issues in treatment outcome definitions for nontuberculous mycobacterial pulmonary disease.** *Euro Respir J.* 2019;53:1801636.	https://pubmed.ncbi.nlm.nih.gov/30819812/
Griffith D, et al. **Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT). A Prospective, Open-Label, Randomized Study.** *Am J Respir Crit Care Med*. 2018;198:1559-1569.	https://pubmed.ncbi.nlm.nih.gov/30216086/

Kamii Y, et al. **Adverse reactions associated with long-term drug administration in *Mycobacterium avium* complex lung disease.** *Int J Tuberc Lung Dis.* 2018;22:1505-1510.	https://pubmed.ncbi.nlm.nih.gov/30606324/
Swenson C, et al. **Clinical Management of Respiratory Adverse Events Associated With Amikacin Liposome Inhalation Suspension: Results From a Patient Survey**. *Open Forum Infect Dis*. 2020;7:ofaa079.	https://pubmed.ncbi.nlm.nih.gov/32322600/