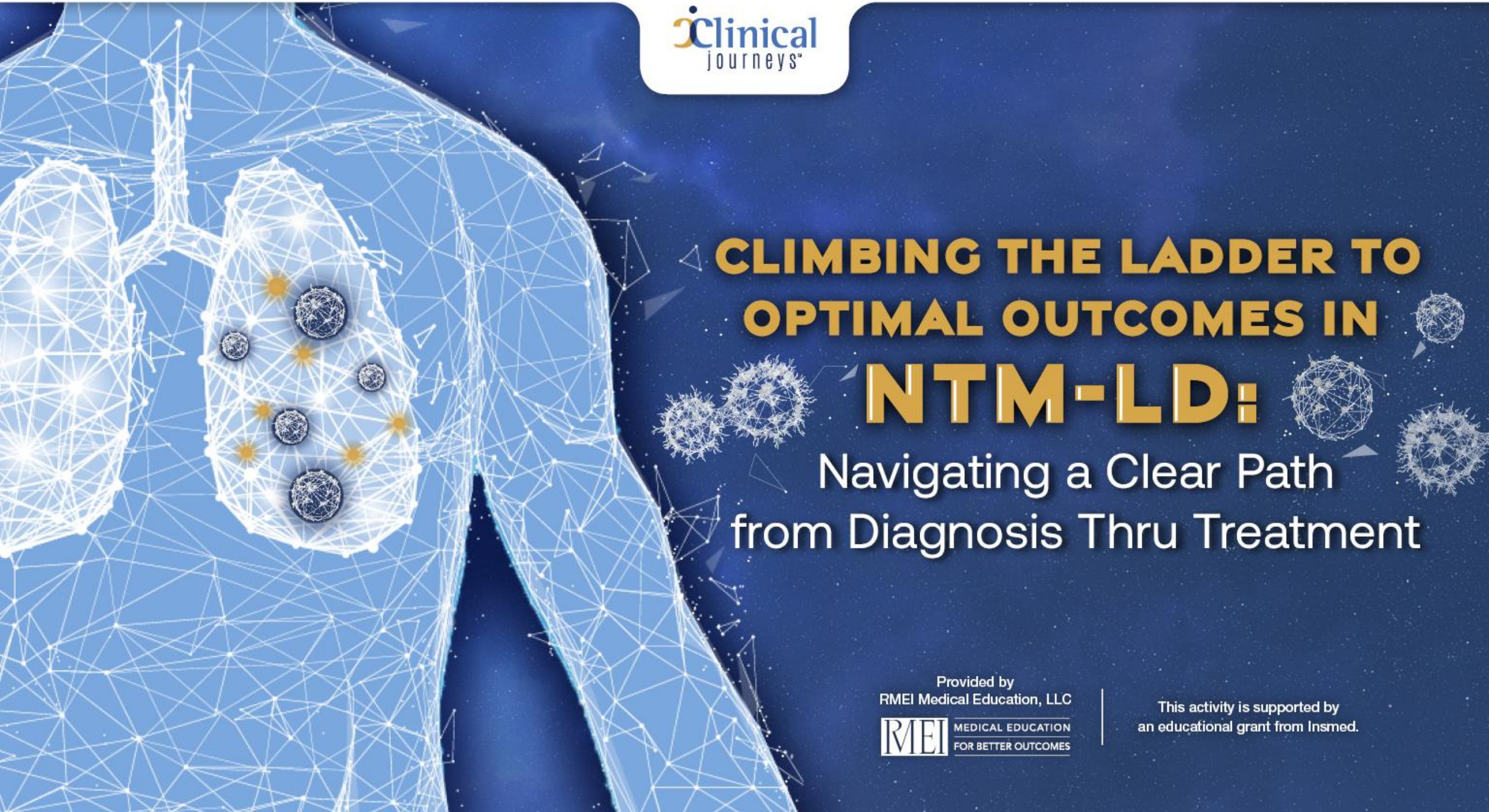
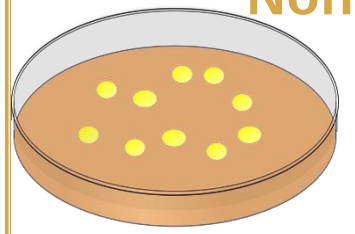

Clinical journeys™
CLIMBING THE LADDER TO OPTIMAL OUTCOMES IN
NTM-LD:
Navigating a Clear Path from Diagnosis Thru Treatment
Provided by
RMEI Medical Education, LLC
RMEI MEDICAL EDUCATION FOR BETTER OUTCOMES
This activity is supported by an educational grant from Insmed.

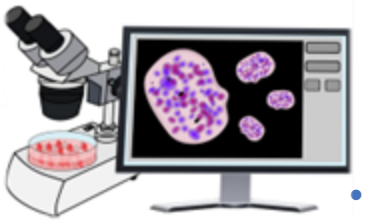
Nontuberculous Mycobacterial Lung Disease

Nontuberculous Mycobacteria (NTM)



- Aerobic bacteria ubiquitously found in soil and water that cause human infection
- More than 200 species
- Lung disease (NTM-LD) only occurs in susceptible hosts

Common NTM Species that Cause Lung Disease in the United States[1,2]



- *Mycobacterium avium* complex (MAC) accounts for 80% of all NTM-LD
  - *M. avium*
  - *M. intracellulare*
  - *M. intracellulare* subspecies *chimaera*
- *M. kansasii*
- *M. abscessus (subsp: abscessus, massiliense, boletti)*

Burden of NTM-LD

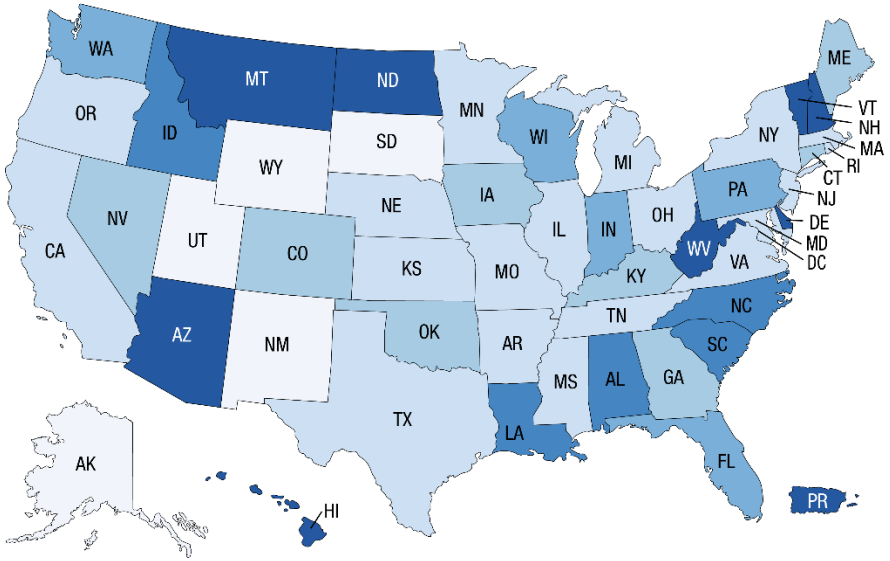
- Physical and social functioning, general health
- Pain and fatigue
- 3X ↑ increased risk for all-cause hospitalization compared to controls[3]
- **41%** Patients with MAC-LD experiencing **radiographic decline** over a median follow-up of ~5 years[4]
- **4.3X** Incidence of **respiratory failure**[5]
- **35%** 5-year all-cause **mortality** in patients with NTM isolates[6]

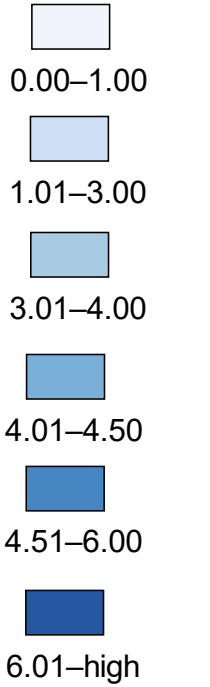
1. Prevots DR, et al. *Clin Chest Med.* 2015;36(1):13-34.
2. Tortoli E, et al. *Infect Genet Evol*. 2019;75:103983.
3. Diel R, et al. *Eur Respir J.* 2017;49(4):16021209.
4. Gochi M, et al. *BMJ Open.* 2015;5(8):e008058.
5. Yeh J, et al. *PLoS One.* 2014;9(6):e99260.
6. Novosad SA, et al. *Ann Am Thorac Soc.* 2017;14(7):1112-1119.

Clinical journeys℠

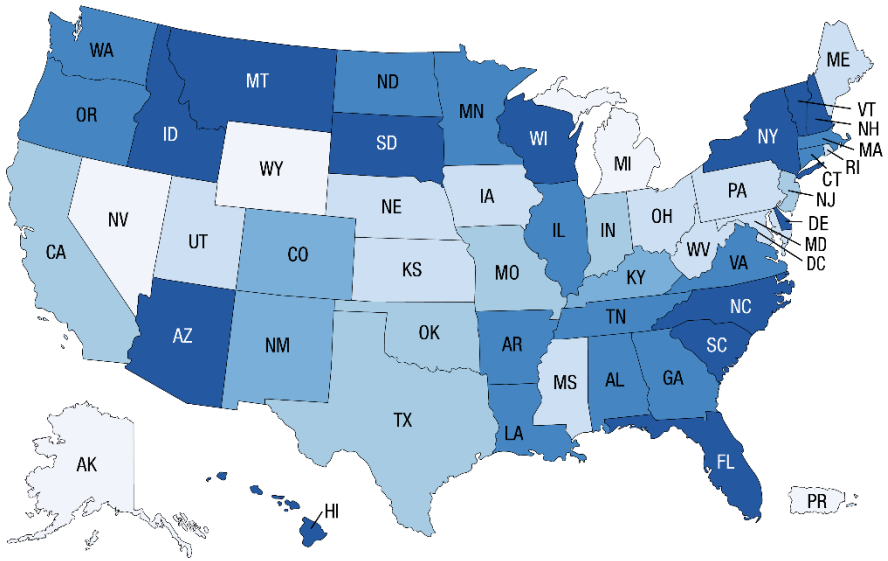
NTM-LD: A Growing Health Issue

NTM Incidence, 2008*





NTM Incidence, 2015*



NTM-LD is now more common than tuberculosis in the United States

**Number of cases per 100,000 persons/years*

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

Impact of Diagnostic Delay on Patients with NTM-LD

- Inappropriate treatment resulting in the development of antibiotic resistance
- Diminished quality of life
- Decreased lung function
- Progression to chronic disease

NTM-LD Patient Experience Survey Findings:[1]

~ 20%

Proportion of patients who felt they were not diagnosed in a timely manner

~ 10%

Proportion of patients who were initially misdiagnosed

1. NTM-LD Patient Experience Survey. Data on File:RMEI.

Polling Question

How confident are you in your ability to readily recognize patients in whom there should be an increased index of suspicion for NTM-LD?

A. Not at all confident
B. Somewhat confident
C. Moderately confident
D. Very confident
E. Completely confident

Patient Story: David

- 66-year-old African American male, widowed
- Retired at the end of 2019
- Enjoys gardening, playing golf, and spending time with his 4 grandchildren

David: Recent Medical History

Chest Infections

2 to 3 per year beginning in mid-2019

Increasingly Persistent Symptom

- Cough with occasional hemoptysis
- Daily yellow sputum production
- Wheezing
- Dyspnea on exertion
- Fatigue

None of the infections could be attributed to COVID-19

Clinical journeys℠

David: Prior Medical History

Former smoker: ~25 pack/years

Diagnosed with COPD at age 59

Managed with formoterol and budesonide

Symptomatic benign prostatic hypertrophy

COPD, chronic obstructive pulmonary disease

Risk Factors for NTM-LD

Pulmonary

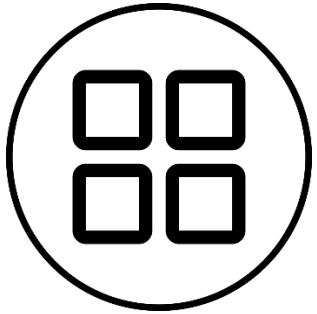
- Bronchiectasis
- COPD
- Cystic fibrosis
- Asthma
- Alpha-1 antitrypsin deficiency
- Prior infections like TB
- GERD with micro-aspiration

Medications

- Immunosuppressants used in HCT and SOT patients
- Biologic agents (eg, anti-TNF agents) used to treat Inflammatory disorders
- Inhaled corticosteroids

Immunologic

- Chronic granulomatous disease
- Common variable immunodeficiency
- HIV infection
- Hematologic and lymphoproliferative malignancy



Other

- Exposure/transmission: Gardening, Hot tubs, etc
- Body type: Tall, thin, scoliosis and/or pectus excavatum
- Gender: Female
- Race: Caucasian

GERD, gastroesophageal reflux disease; HCT, hematopoietic cell transplantation; SOT, solid organ transplantation

Stout JE, et al. *Int J Infect Dis.* 2016;45:123-134; Andréjak C, et al. *Thorax.* 2013;68(3):252-262; Szymanski EP, et al. *Am J Respir Crit Care Med.* 2015;192(5):618-628.

Clinical journeys

David: Pulmonology Work-Up

Chest CT

- Extensive diffuse nodular tree-in-bud infiltrates
- Consolidation without cavitation
- Cylindrical bronchiectasis with mucous plugging

Sputum Cultures

- Two separate sputum samples were smear and culture positive *M. avium* complex

Other Tests

- Unremarkable

Clinical journeys℠

2020 ATS/ERS/ESCMID/IDSA Clinical Practice Guidelines for Diagnosis

CLINICAL

- Pulmonary or systemic symptoms: Cough, fatigue, weight loss, dyspnea, hemoptysis, fever
- Exclusion of other diagnoses

RADIOLOGIC

- Chest radiograph or CT evidence of the following: Nodular infiltrate, tree-in-bud inflammation, or cavitary opacities

MICROBIOLOGIC

- With ≥2 expectorated sputum samples → 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

All criteria must be met for diagnosis

Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913.

David: Diagnosis of NTM-LD

David was diagnosed with NTM-LD in late 2021 based on his:

- ✓ Clinical symptoms
- ✓ Chest CT findings
- ✓ Positive sputum cultures

Polling Question

Which of the following *best* describes your approach to managing newly diagnosed patients with NTM-LD?

- Watchful waiting until symptoms and radiologic findings worsen
- Empirical antimicrobial therapy based on disease type (nodular-bronchiectactic versus cavitary)
- Airway clearance in combination with empirical antimicrobial therapy based on disease type
- Antimicrobial therapy guided by susceptibility testing
- Airway clearance in combination with antimicrobial therapy guided by susceptibility testing

Clinical journeys℠

Patient Story Recap: David

- Retired, 66-year-old widowed, African American Male
- Diagnosed with NTM-LD in late 2021 based on the development of chronic symptoms, radiologic findings, and multiple positive sputum cultures following a ~2.5-year history of recurrent chest infections

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 acid-fast bacilli sputum smears and/or cavitary lung disease** (conditional recommendation, very low certainty in estimates of effect)**.**

- Over 50% of patients who meet diagnostic criteria for NTM-LD progress within 3 to 5 years

Host/demographic Factors

- Male gender
- Older age
- Presence of co-morbidities
- Low body mass index

Laboratory Factors

- Elevated inflammatory indices (ESR, CRP)
- Anemia
- Hypoalbuminemia

Radiographic Factors

- Fibrocavitary
- Extent of disease

Bacteriologic Factors

- Bacterial load
- NTM species

Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913; Kwon BS, et al. *Resp Med*. 2019;150:45-50; Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535; Moon SM, et al. *Resp Med*. 2019;151:1-7; Hwang JA, et al. *Eur Respir J.* 2017;49(3):1600537.

Recommended Treatment Regimens for MAC-LD

Type of Disease	No. of Drugs	Preferred Regimen[a]	Dosing Frequency
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampin (rifabutin) Ethambutol Amikacin IV[b]	Daily (IV aminoglycoside may be used 3 times weekly)
Refractory	≥4	Azithromycin (clarithromycin) Rifampin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV[b]	Daily (IV aminoglycoside may be used 3 times weekly)

[a] Alternative drugs could include clofazimine, moxifloxacin, linezolid (tedizolid), bedaquiline

[b] Consider for cavitary, extensive nodular bronchiectatic, or macrolide resistant disease

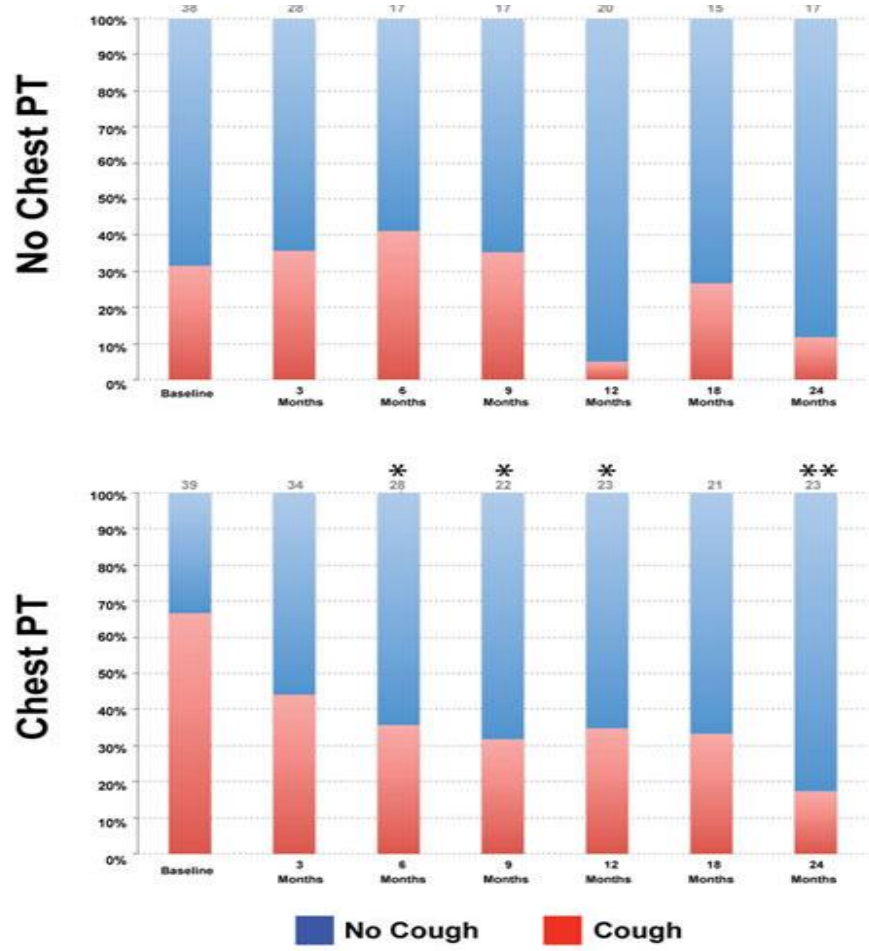
Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

Impact of Airway Clearance Modalities on NTM-LD

Airway Clearance

- Regular exercise
- Vibratory PEP
- Chest percussion
- Nebulized hypertonic saline
- Chest wall oscillation

Retrospective Study of Chest Physiotherapy in NTM-LD Patient Not Receiving Antibiotics



Basavaraj A, et al. *Int J Respir Pulm Med*. 2017;4(1):065.

Clinical journeys

David: Initial Treatment of NTM-LD

Antibiotic Regimen

Thrice weekly:

- Azithromycin
- Ethambutol
- Rifabutin

Airway Clearance Regimen

- Exercise
- Deep breathing with huff cough
- Nebulized hypertonic saline
- PEP therapy

3 Months Treatment

- Significant symptomatic improvement
- Minimal CT improvement
- Sputum cultures remained positive
- Lost 10 lbs since starting treatment due to nausea and decreased intake

Clinical journeys℠

Polling Question

How confident are you in your ability to educate your patients with NTM-LD about potential antimicrobial therapy adverse effect and utilize appropriate strategies for monitoring and mitigation?

A. Not at all confident
B. Somewhat confident
C. Moderately confident
D. Very confident
E. Completely confident

Monitoring for Adverse Drug Reactions

Adverse reactions are very common during the course of therapy and can lead to:
Interruption in treatment, morbidity, and in some cases nonadherence and discontinuation of therapy

Macrolide	Ethambutol	Rifampin	Amikacin
• QT prolongation • GI side effects • Hearing loss • Hepatotoxicity	• Optic neuritis • Neuropathy	• Cytopenias • GI intolerance • Hypersensitivity • Hepatoxicity	• Renal • Vestibular • Ototoxicity

- Monitoring should be individualized based on treatment regimen, age, comorbidities, concurrent drugs, overlapping drug toxicities, and resources
- CBC, liver function tests, metabolic panel every 1 to 3 months

Amikacin Liposome Inhalation Suspension
Above plus: • Dysphonia • Cough • Shortness of breath

Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913.
Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

Strategies to Mitigate Adverse Effects

- Educate patients regarding potential reactions and monitoring for them
- Switching from one agent to another may be considered in case of intolerance (eg, switching from azithromycin to clarithromycin or vice versa)
- For nausea:
  - Dosing at night instead of in the morning
  - Using anti-emetics
- Rapid identification and management of an adverse reaction may:
  - Decrease the risk of treatment for the patient
  - Improve the chances of treatment completion

NTM-LD Patient Experience Survey Findings:

~ 15%

Proportion of patients who felt their provider had not educated them about the adverse effects of the medications they were taking

~ 15%

Proportion of patients who felt their NTM-LD treatment regimen was not safe

Stout JE, et al. *Int J Infect Dis.* 2016;45:123-134; Daley CL, et al. *Clin Infect Dis.* 2020;71(4):905-913; Haworth CS, et al. *Thorax.* 2017;72(Suppl 2):ii1-ii64. NTM-LD Patient Experience Survey. Data on File:RMEI

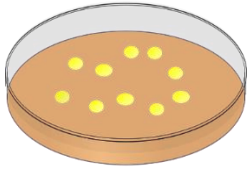
David: Changes to Treatment of NTM-LD

Changes to Treatment Regimen

- Rifabutin replaced with rifampin
- Dosed rifampin before bedtime
- Prescribed an antiemetic
- Nausea mitigated

6 Months After Treatment Switch

- Significant symptomatic improvement
- Noticeable CT improvement
- Sputum cultures remained positive



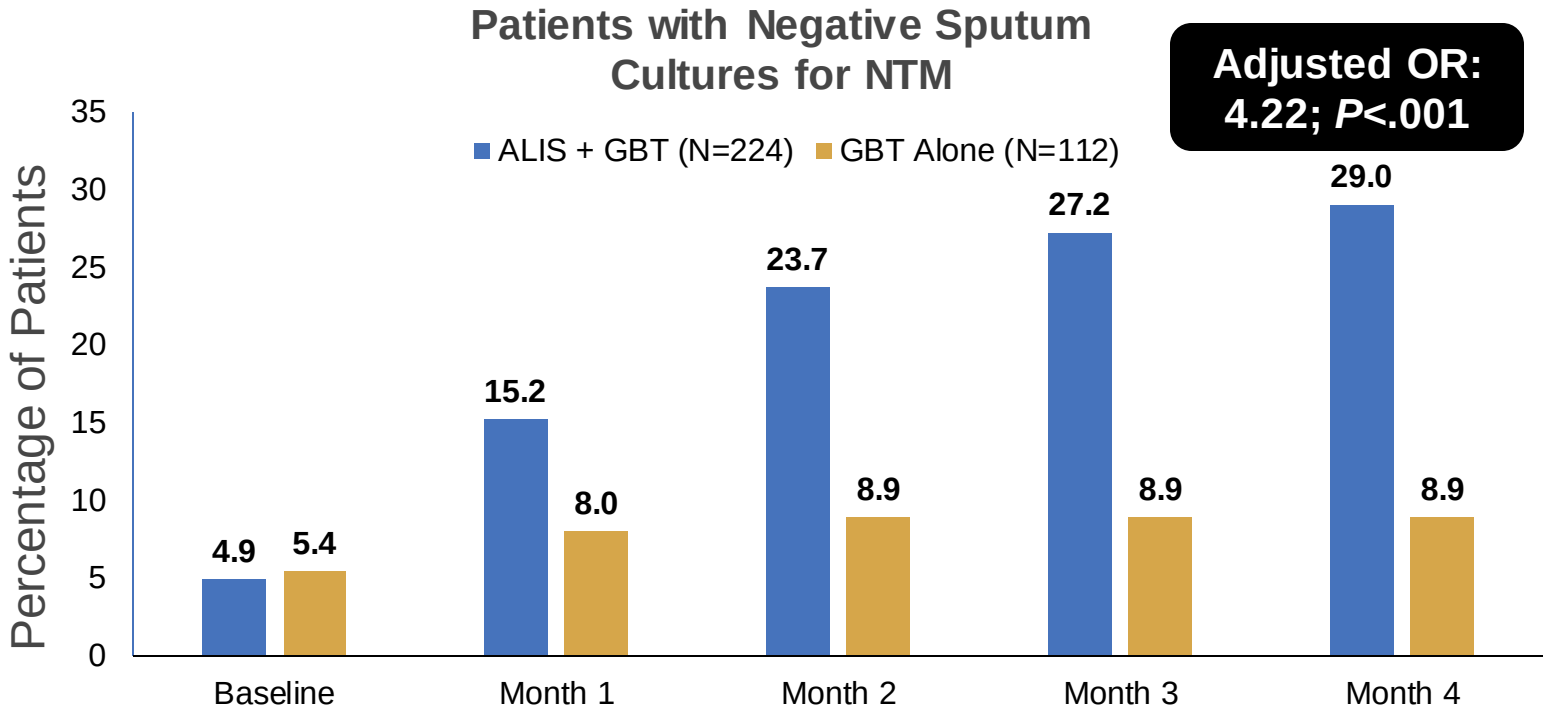
Susceptibility Testing

- Macrolide and amikacin sensitive
- Decision made to add ALIS to regimen in October 2022

Clinical journeys℠

Phase III CONVERT Study: ALIS for Refractory MAC Lung Disease

- N=336
- Refractory MAC lung disease
- Randomized 2:1 to receive either ALIS + GBT or GBT alone



Adjusted OR: 4.22; *P*<.001

Guideline Recommendation

In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, we recommend the addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen, only.
(Strong recommendation, moderate certainty in estimates of effect.)

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy

Griffith DE, et al. *Am J Respir Crit Care Med.* 2018;198(12):1559-1569. Daley CL, et al. *Clin Infect Dis*. 2020;71(4):905-913. Daley CL, et al. *Eur Respir J*. 2020;56(1):2000535.

CONVERT Study
12-month Open-label Extension Trial

		Culture Conversion		Adverse Reactions		
Cohort	N	By Month 6	By Month 12	SAE	Respiratory	Hearing Decline
ALIS-naive	90	26.7%	33.3%	35.6%	83.3%	7.8%
Prior ALIS*	73	9.6%	13.7%	27.4%	46.6%	9.6%

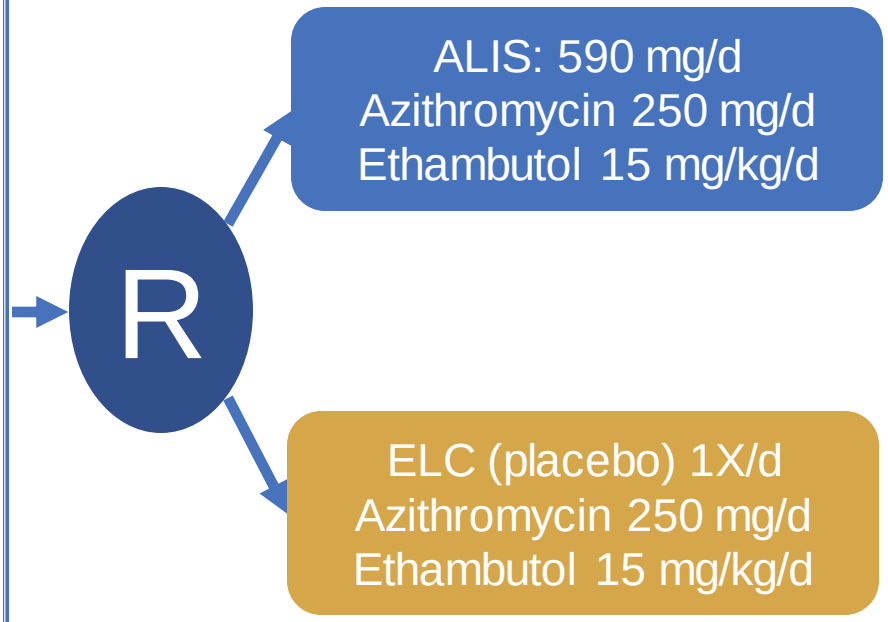
*Up to 8 months of ALIS

- Conversion was sustained and durable in more patients treated with ALIS plus GBT for 12 months after conversion than in those treated with GBT alone. No new safety signals were associated with 12 months of treatment after conversion.

Winthrop KL, et al. *Ann Am Thorac Soc.* 2021;18(7):1147-1157. Griffith DE, et al. *Chest.* 2021;160(3):831-842.

ENCORE: Phase 3 Study of ALIS-based Regimen for *Newly Diagnosed* MAC NTM-LD[1]

- N=250
- ≥18 years of age
- Current diagnosis of MAC lung infection.
- Chest CT within 6 months prior to screening to determine presence and size of pulmonary cavities
- No prior mycobacterial antibiotic treatment for current MAC lung infection



1° Endpoint

- Δ in RSS (b-line to month 13)

Selected 2° Endpoints

- % patients achieving durable culture conversion at month 15
- Δ in in FSS (b-line to month 13)
- % patients achieving culture conversion by month 12
- % patients achieving culture conversion by month 6
- % patients achieving culture conversion during treatment (B-line to month 12)
- Time to culture conversion (B-line to month 12)

Randomized Phase 3 ARISE study is also underway to validate patient-reported outcome instruments in adult subjects with newly diagnosed NTM-LD caused by MAC.[2]

ELC, empty liposome control; RSS, respiratory symptom score

1. www.clinicaltrials.gov. NCT04677569.
2. www.clinicaltrials.gov. NCT04677543.

Clinical journeys℠

Polling Question

How often do you add ALIS to antimicrobial regimens in your patients with refractory NTM-LD?

A. Never
B. Rarely
C. Sometimes
D. Often
E. Always

David: Conclusion

Treatment Regimen

- Experienced some hoarseness after switch to ALIS, but it eventually subsided

5 Months After Switch

- Symptoms occasional and mild
- Marked CT improvement
- Sputum cultures negative
- Continuing treatment until cultures are negative for 12 months

Summary

- NTM-LD is increasingly common globally and associated with chronic lung conditions
- Recognition of risk factors for NTM-LD and application of current clinical, radiographic, and microbiologic criteria for diagnosis
- NTM-LD is manageable
- Robust communication with the patient is essential regarding the goals NTM-LD treatment, as well as the benefits and risks of treatment
- Effective mitigation strategies for NTM-LD medication adverse effects include prompt medication adjustments and scheduled monitoring
- Utilizing susceptibility testing helps guide and personalize treatment at the start of treatment, as well as during treatment when needed

Clinical journeys℠

Thank you!

Please remember to complete the post-test and evaluation to receive CE credit

Clinical journeys℠