Nontuberculous Mycobacterial Lung Disease – Challenges in Diagnosis and Treatment

Daniel A. Solomon, MD
Physician, Division of Infectious Diseases
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

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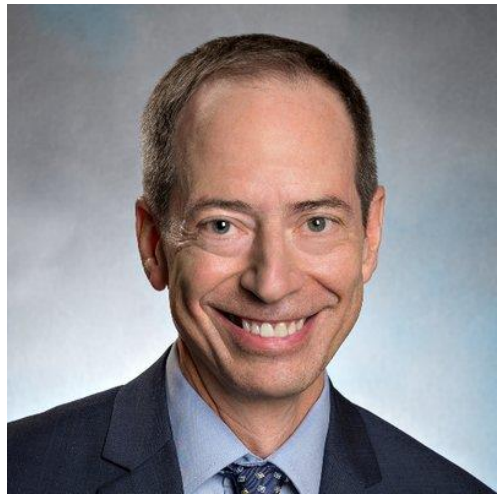
Disclosures

None

Acknowledgements



Paul Sax, MD

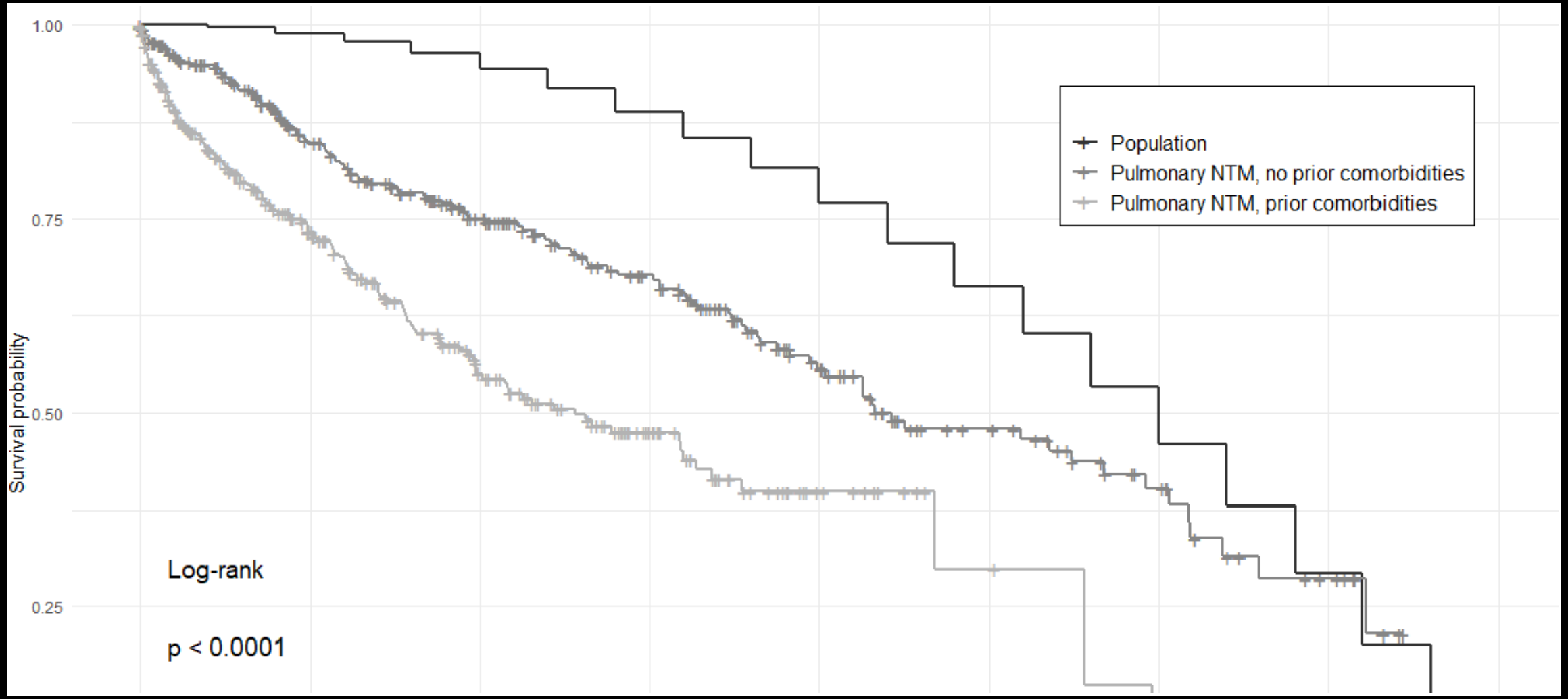
Ruvandhi Nathavitharana, MD

Rocio Hurtado, MD

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

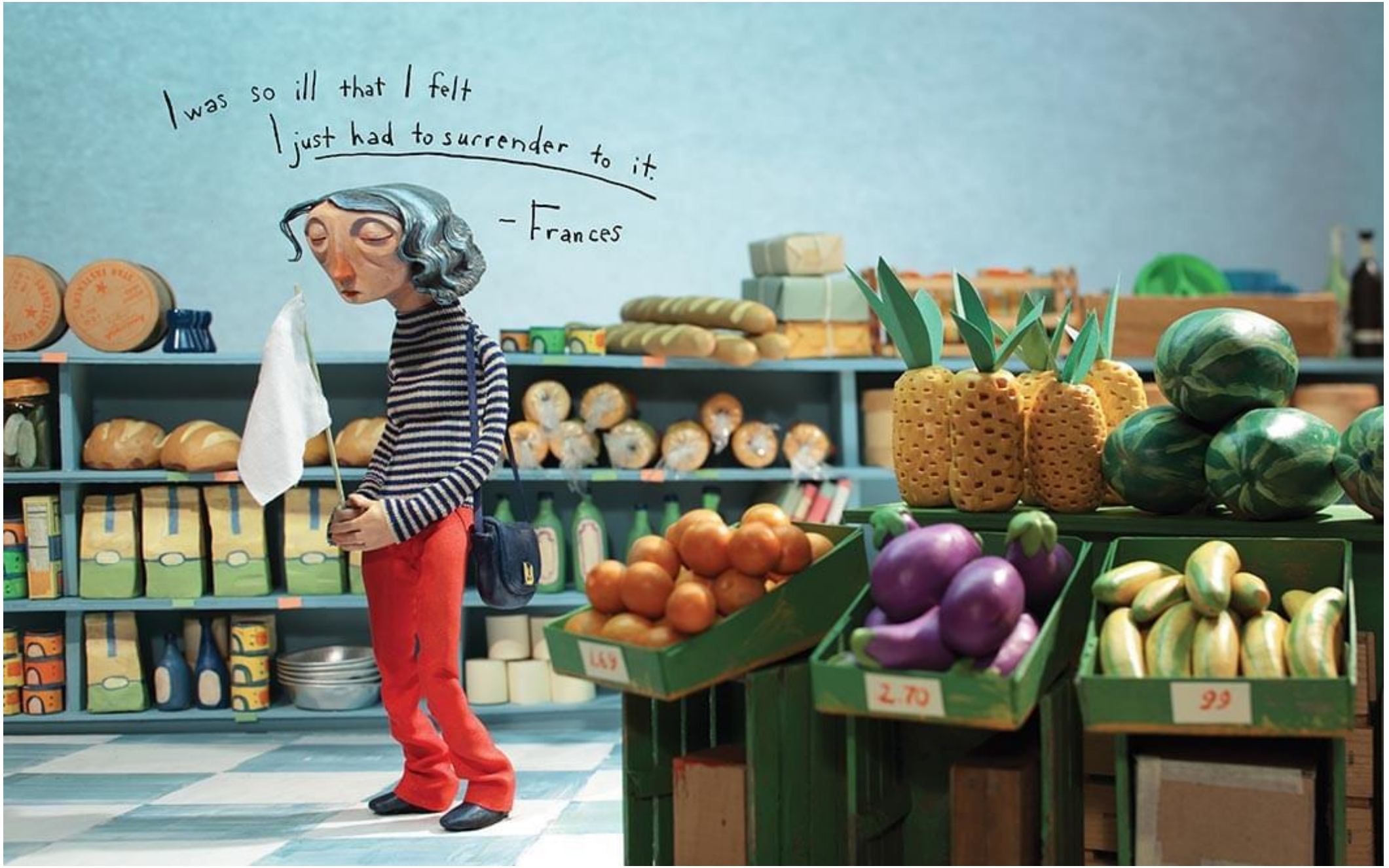
Charles L. Daley,[1,2,a] Jonathan M. Iaccarino,[3] Christoph Lange,[4,5,6,7,a] Emmanuelle Cambau,[8,a] Richard J. Wallace, Jr,[9,a] Claire Andrejak,[10,11] Erik C. Böttger,[12] Jan Brozek,[13] David E. Griffith,[14] Lorenzo Guglielmetti,[8,15] Gwen A. Huitt,[1,2] Shandra L. Knight,[16] Philip Leitman,[17] Theodore K. Marras,[18] Kenneth N. Olivier,[19] Miguel Santin,[20] Jason E. Stout,[21] Enrico Tortoli,[22] Jakko van Ingen,[23] Dirk Wagner,[24] and Kevin L. Winthrop[25]

Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.



Diagnosis of NTM pulmonary disease associated with reduced survival

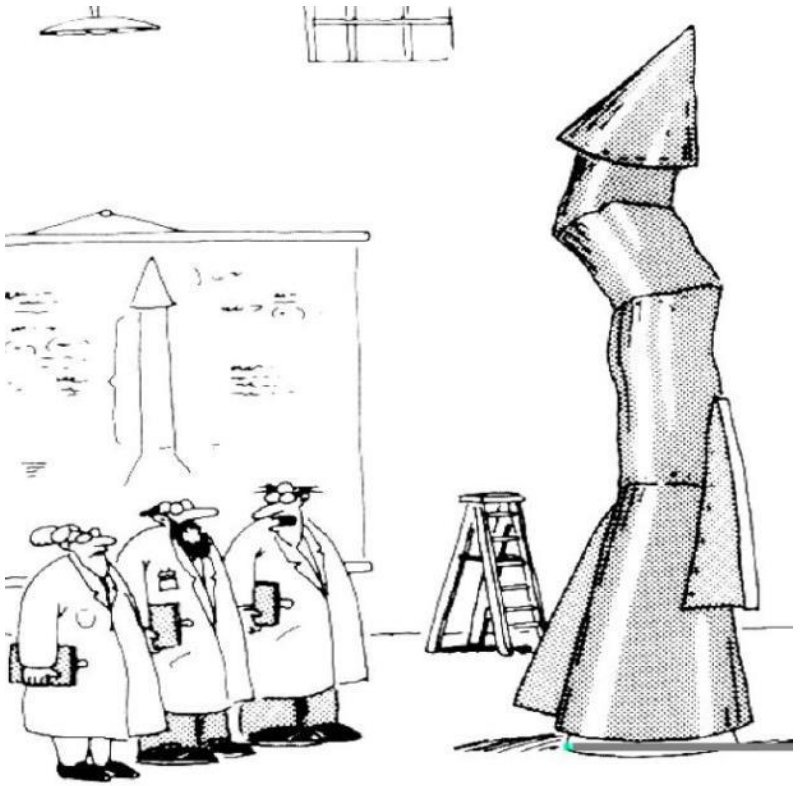
Mourad A, et al Clinical Infectious Diseases 2020.



https://www.ntmfacts.com/a-thousand-words-gallery/

NTM lung disease – Why so difficult?

- Nomenclature confusing
- Disease spectrum broad
- Host susceptibility irreversible
- Environmental reservoir
- Diagnosis challenging
- Treatments complex, poorly tolerated, long
- Few controlled clinical trials



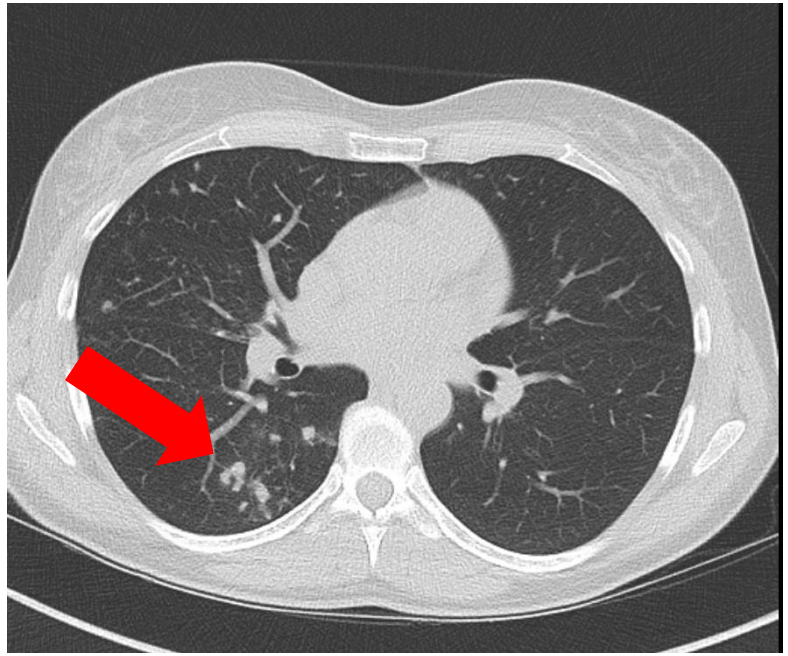
"It's time to face reality, my friends... We're not exactly rocket scientists."

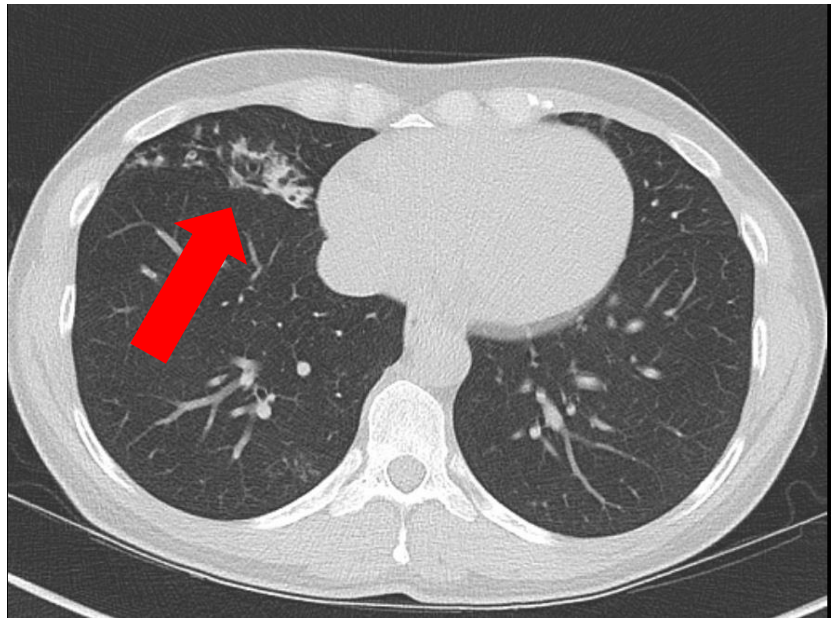
Goals of this presentation

- Review NTM terminology
- How to make the diagnosis?
- Treatment: Who? When?
- How to select an initial regimen?
- How to counsel patients?

Case

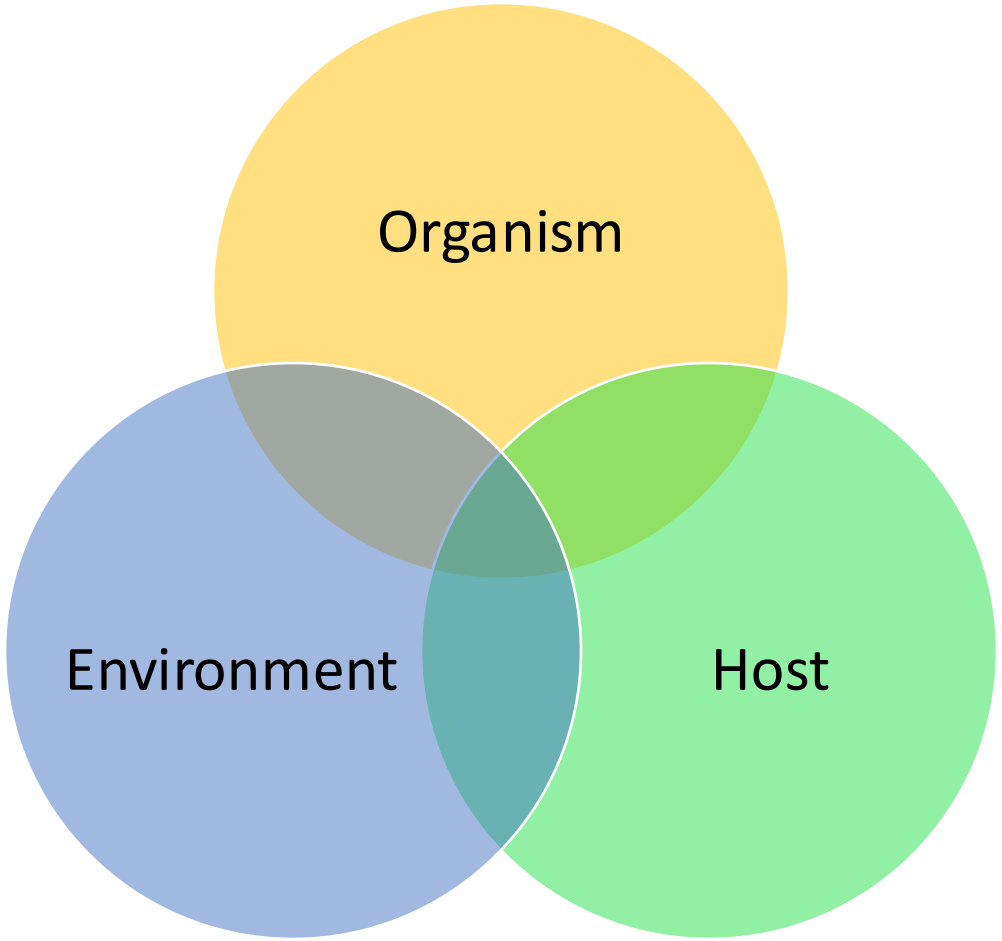
- 61-year-old woman presents with persistent cough
- PMHx: Frequent episodes of “bronchitis”, requires antibiotics
- SHx: Smoked briefly in her 20s; avid gardener
- PE notable for O2 sat 98%, weight 104 lbs, BMI 18.4
- CT chest demonstrates bronchiectasis and tree-in-bud nodularity at the bases R > L
- Expectorated sputum AFB smear negative; mycobacterial culture grows *M intracellulare*





Does this patient have NTM infection?

1. Yes
2. No
3. Maybe



Ranatunga, Front Immunol 2020

NTMs: Defined by what they are not!

Organism

- Tuberculous mycobacteria:
  - *Mycobacterium tuberculosis*
  - *Mycobacterium leprae*

- NTMs – *all* the rest, approximately 200 species!
- Most common causes of pulmonary disease
  - *M avium* complex* (~80%)
  - *M kansasii* (~5-10%)
  - *M abscessus* (~5-10%)
  - *M xenopi, M fortuitum, M malmoense*, others

Prevots DR, et al. Am J Respir Crit Care Med. 2010;182:970-976.

Slow vs. “Rapid” growers

Organism

- Slow growers
  - ***M avium* complex**
    - *M avium*
    - *M intracellulare*
    - *M chimaera*
  - *M kansasii*
  - *M xenopi*
  - *M malmoense*

- Rapid growers*
  - ***M abscessus* group**
    - *M abscessus*
    - *M bolleti*
    - *M massilience*
  - *M fortuitum*
  - *M chelonei*

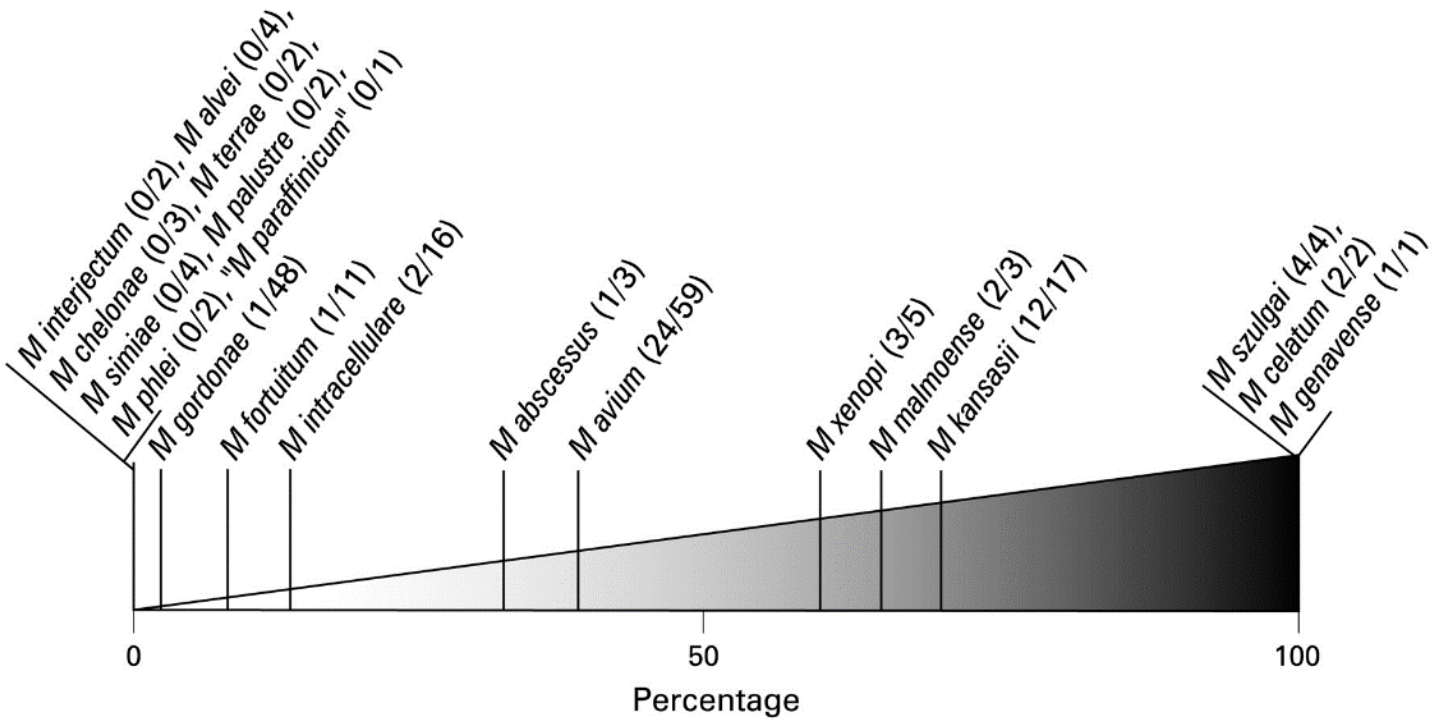
*Grows in culture by 7 days

Organism

Respiratory infection

Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, The Netherlands FREE

J van Ingen[1,2], S A Bendien[1], W C M de Lange[1], W Hoefsloot[1], P N R Dekhuijzen[1], M J Boeree[1], D van Soolingen[2]



Thorax 2009;64:502-506

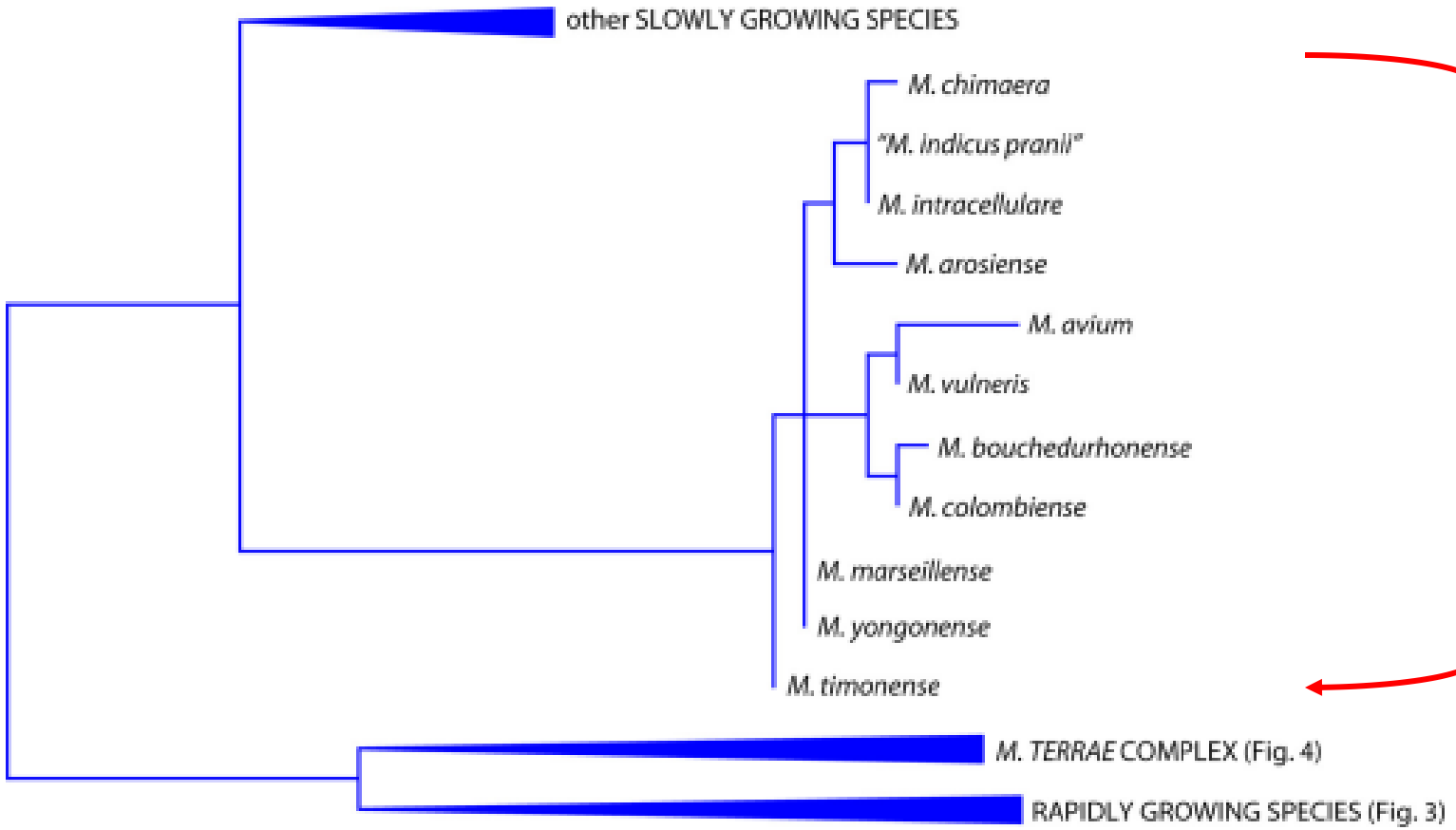
Outcomes differ by species

Organism

NTM	Expected Cure
M kansasii	95%
M avium complex	56%-85%, depends on extent of disease and macrolide susceptibility; 30% relapse
M abscessus group	25% if macrolide resistant, up to 80% if sensitive

Mycobacterium avium complex (MAC)

Organism



MAC

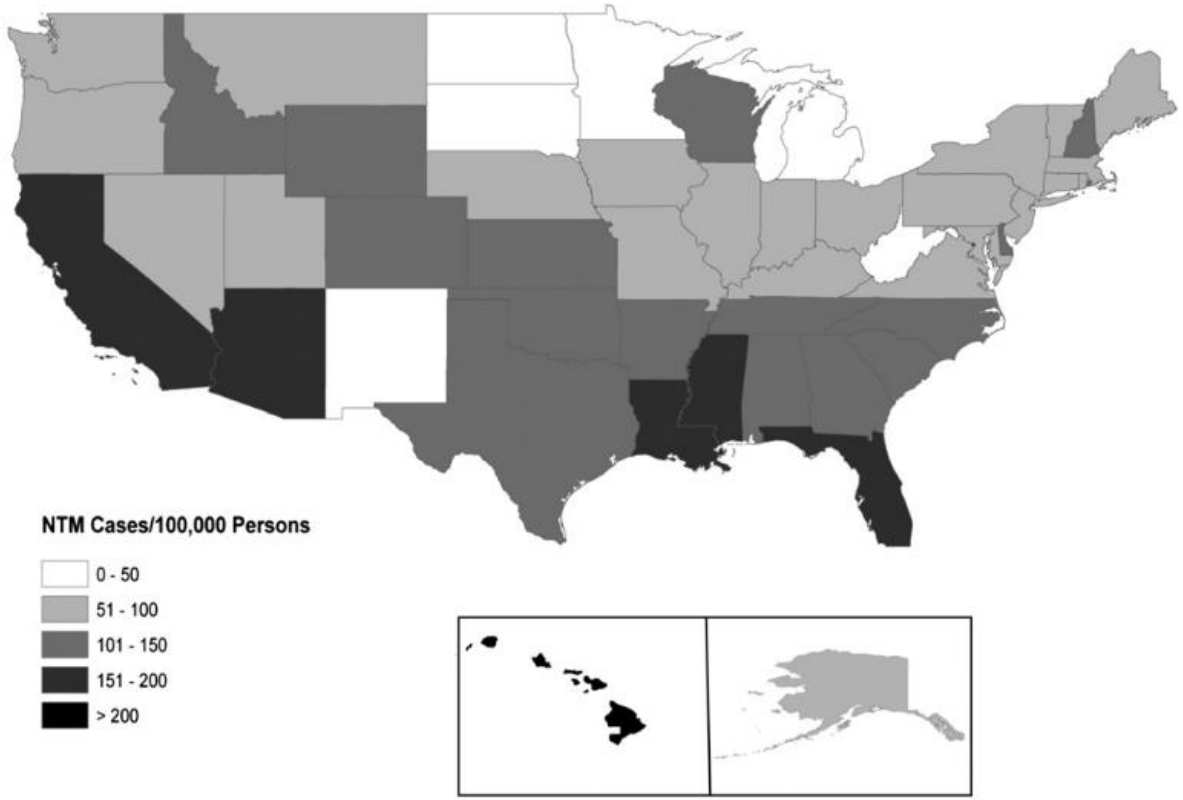
FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

MAC: species matters

Organism

- Pathogenicity: M. intracellulare > M. avium > M. chimaera
- M. intracellulare presents with more advanced disease
- M. chimaera and M. avium may have a higher rate of clinical recurrence
- Overall MAC cure rates ~60-80%

Prevalence of pulmonary NTM differs by geographic location and proximity to water



Environment

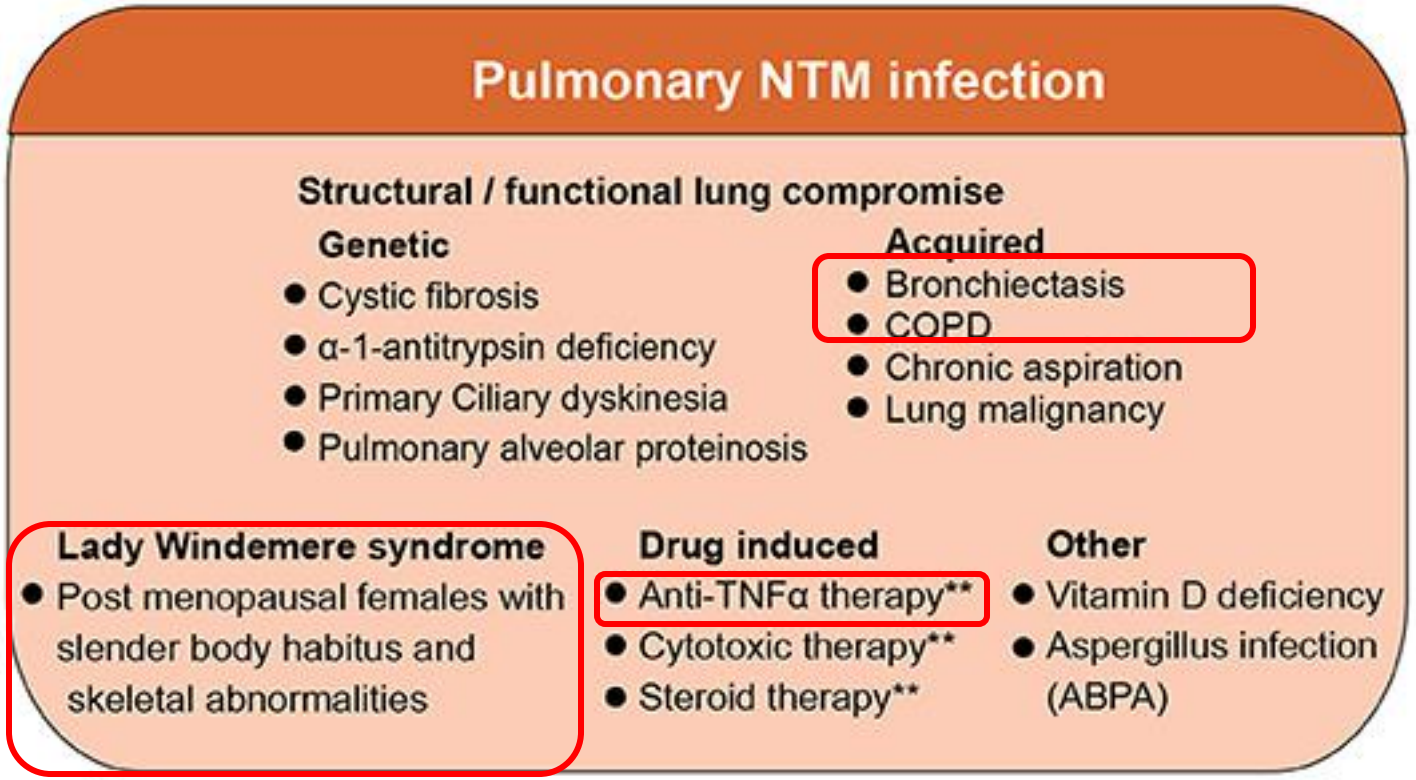
Adjemian J, et al. Am J Respir Crit Care Med. 2012;185:881-886.

How do patients acquire pulmonary NTM?

- Inhalation the dominant route
- Water aerosols the most likely source
  - Showers
  - Water taps
  - Hot tubs, spas, pools
  - Humidifiers
  - HVAC systems
- Dust, potting soil
- Aspiration, reflux

Risk Factors for NTM infections

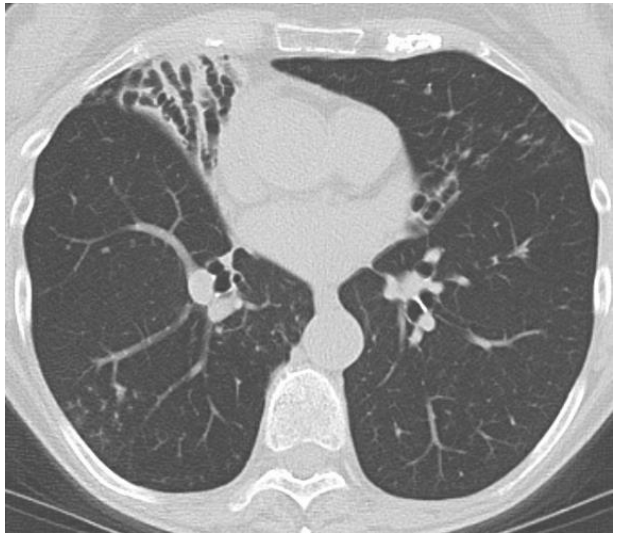
Host



- COPD: 2-10X
- Bronchiectasis: 44-188X

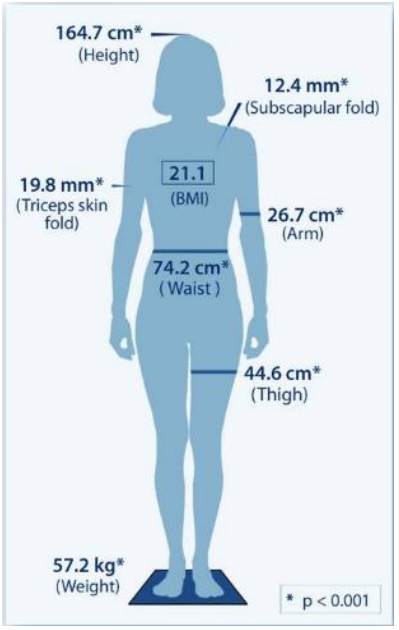
Ranatunga, Front Immunol 2020

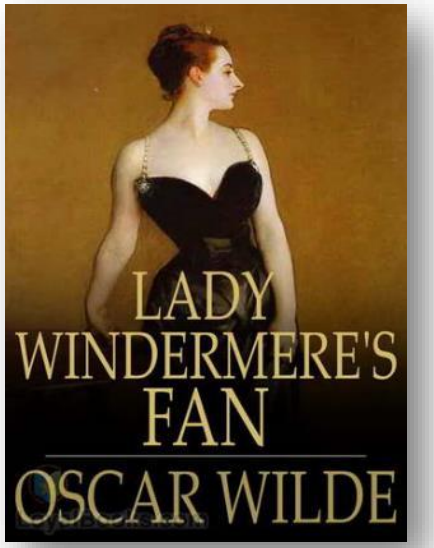
Nodular bronchiectasis



Host

- Thin, post-menopausal women
- Often non-smokers or ex-smokers
- Scoliosis, pectus excavatum
- Slowly progressive
- “Lady Windermere”





Am J Respir Crit Care Med. 2008;178(10):1066–1074.

Clinical and microbiologic criteria for diagnosis of NTM disease

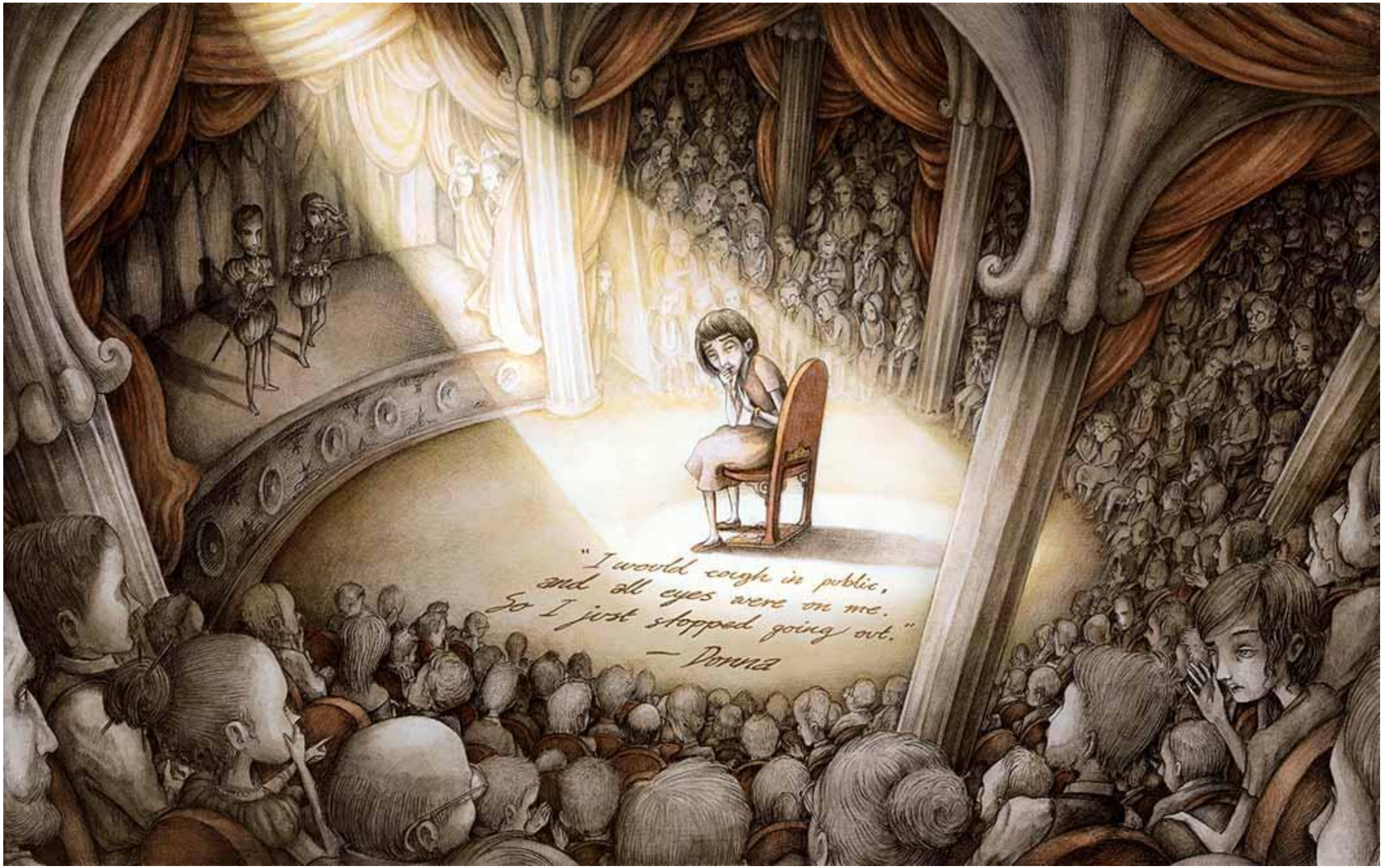
1. Clinical Pulmonary and/or systemic symptoms

Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.

Pulmonary NTMs: Clinical syndrome

- *Highly* variable and frequently non-specific
- Pulmonary symptoms
  - Chronic cough – “can’t bring it up”
  - Episodes of excess sputum production, especially following URIs
  - Dyspnea tends to occur only in advanced disease or with underlying COPD
- Extrapulmonary symptoms
  - Fatigue
  - Low-grade fever, night sweats
  - Weight loss – ominous!

https://www.ntmfacts.com/a-thousand-words-gallery/



https://www.ntmfacts.com/a-thousand-words-gallery/

Clinical and microbiologic criteria for diagnosis of NTM disease

1. Clinical — Pulmonary and/or systemic symptoms
2. Radiologic — Nodular or cavitary opacities on CXR or CT
   Bronchiectasis with small nodules

<u>Two main forms of pulmonary NTM disease</u>

- Nodular bronchiectatis – thin women
- Fibrocavitary – COPD is biggest risk, often high organism burden
- Overlap is common, especially in severe and progressive bronchiectasis

Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.

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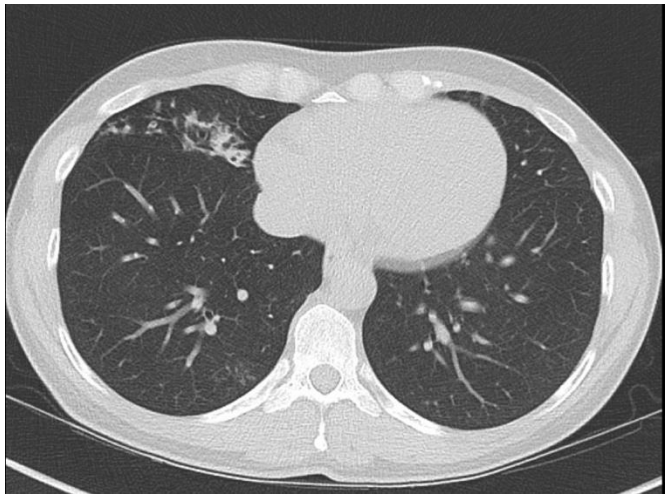

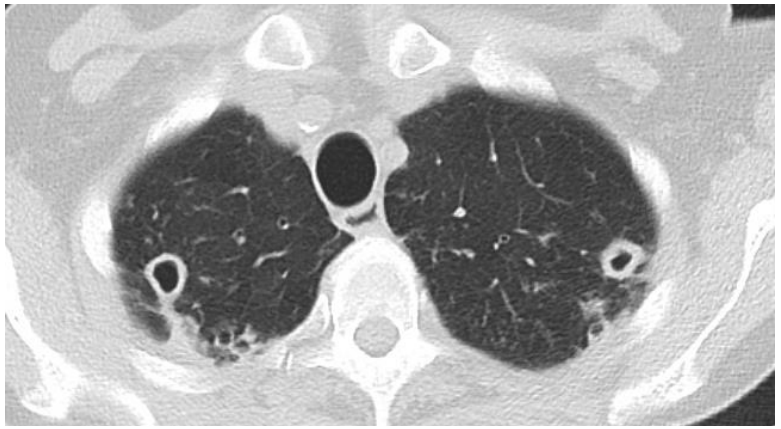

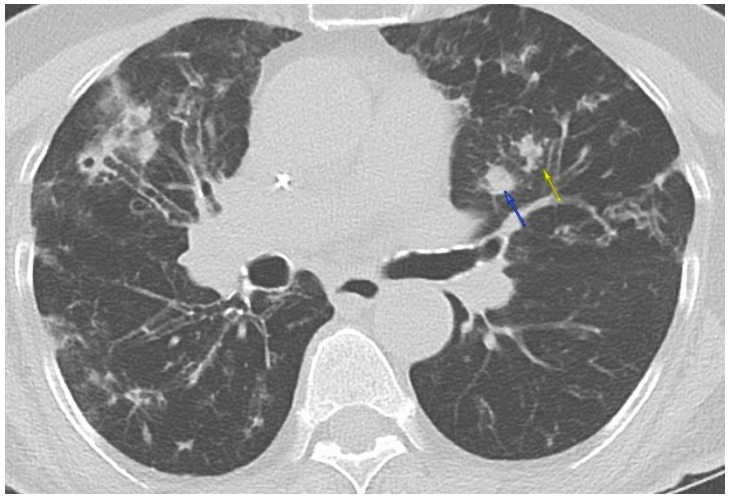

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Clinical and microbiologic criteria for diagnosis of NTM disease

1. Clinical — Pulmonary and/or systemic symptoms
2. Radiologic — Nodular or cavitary opacities on CXR or CT
   Bronchiectasis with small nodules
3. Microbiologic

1. Positive cultures from at least 2 expectorated samples

Or

2. Positive culture from at least 1 BAL

Or

3. Transbronchial or lung biopsy with granuloma and positive culture for NTM

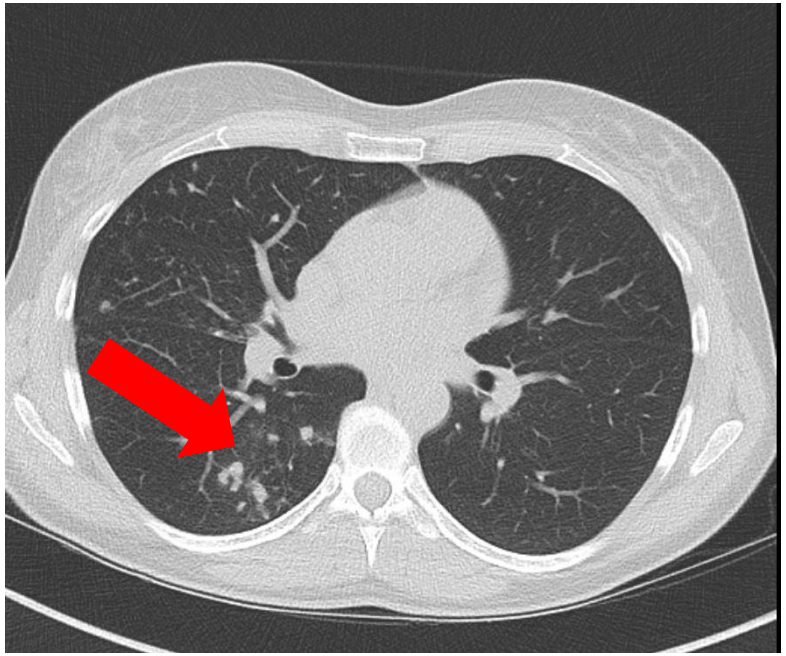
Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.

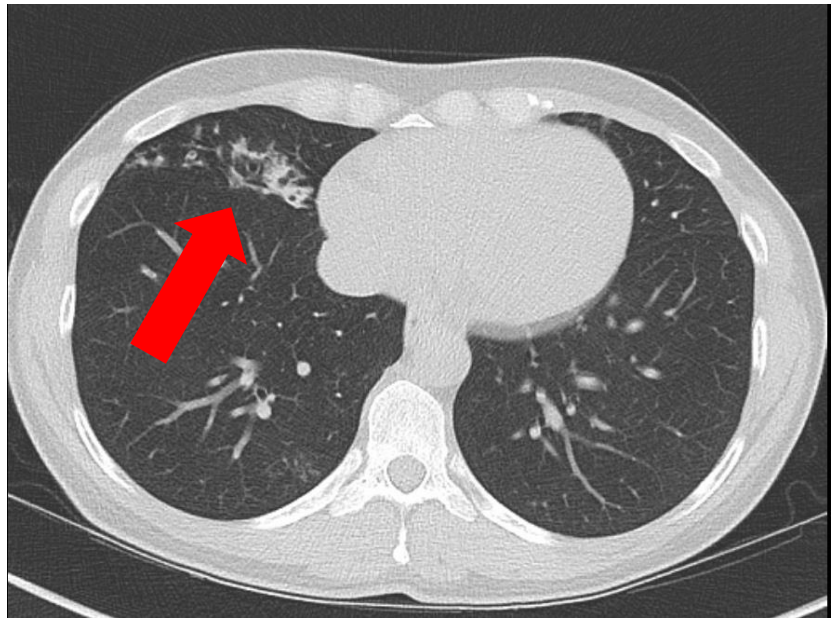
Case

- 61-year-old woman presents with persistent cough
- PMHx: Frequent episodes of “bronchitis”, requires antibiotics
- SHx: Smoked briefly in her 20s; avid gardener
- PE notable for O2 sat 98%, weight 104 lbs, BMI 18.4
- CT chest demonstrates bronchiectasis and tree-in-bud nodularity at the bases R > L
- Expectorated sputum AFB smear negative; mycobacterial culture grows *M intracellulare*

Does this patient have NTM infection?

- Maybe





Case continued

- Undergoes induced sputum exams on 3 separate days
- All are smear-negative for mycobacteria
- 2/3 are culture positive for *M. intracellulare*

Does our case have pulmonary NTM?

Yes!

- Host: Thin postmenopausal woman
- Symptoms: Cough, poor exercise tolerance
- Imaging: Inflammatory nodules, bronchiectasis
- Micro: 2/3 sputum samples positive for MAC

What would you do next?

A. Start 3 drug therapy x12-18 months
B. Await drug susceptibilities then start treatment
C. Active surveillance
D. Depends

*Diagnosis of pulmonary NTM **rarely requires immediate therapy!** A period of observation to collect more data, elicit patient preferences, and monitor clinical course is usually warranted.*

To treat or not to treat?

Guiding data	Favors Treatment
Clinical symptoms	
Radiographic findings	
Burden of infection	
Co-morbidities	
Species isolated	

Consider: drug toxicities, DDIs, duration of treatment

To treat or not to treat?

Guiding data	Favors Treatment
Clinical symptoms	• Intolerable, progressive respiratory symptoms • Weight loss • Progressive sx over time
Radiographic findings	• Fibrocavitary disease • Lung destruction
Burden of infection	• Smear Positive
Co-morbidities	• Immunosuppression, TNF-alpha inhibitors
Species isolated	• *M. kansasii* (high rate of cure) • *M. abscessus* (high morbidity)

Consider: drug toxicities, DDIs, duration of treatment

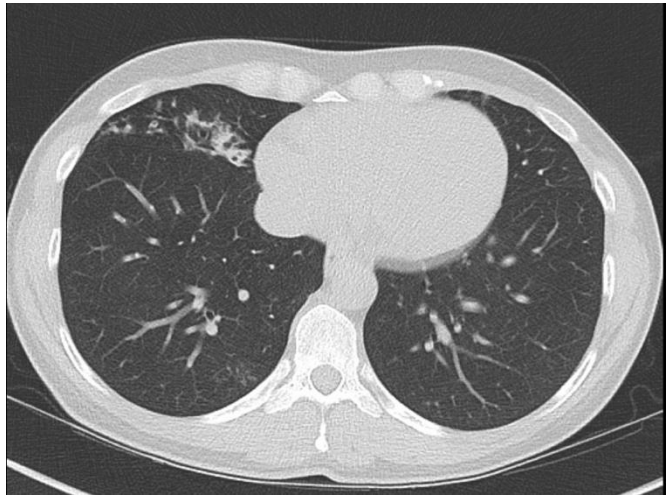
Observation (Active surveillance)

- Mild or intermittent symptoms, nodular bronchiectasis pattern
- Re-evaluate in 6-12 months clinically and with CT scan
  - Expect waxing and waning abnormalities
- Aggressively treat bronchiectasis flares with abx NOT used for NTMs:
  - Amoxicillin-clavulanate
  - TMP/SMX
  - Doxycycline

How the micro lab can help

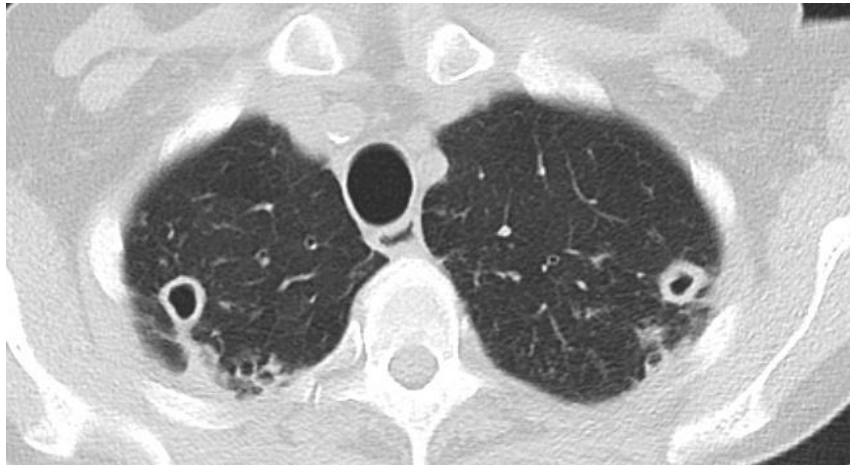
- Reference laboratories with extensive experience:
  - *M avium* complex: National Jewish Health, Denver
  - Rapid-growers such as *M abscessus*: University of Texas Health Science Center
- Key determinant of treatment responsiveness is susceptibility to **macrolides** (azithromycin or clarithromycin)
  - Amikacin and rifampin also useful in certain circumstances
- Remainder of drug susceptibility testing has not been correlated with treatment outcomes!

Treatment of macrolide-susceptible NTM lung disease due to MAC



Mild nodular bronchiectasis

- Azithromcyin, rifampin, ethambutol
- Can give daily or 3x / week



Severe nodular bronchiectasis or fibrocavitary disease

- Azithromycin, rifampin, ethambutol DAILY
- Consider addition of amikacin 3x/week for at least 1 month

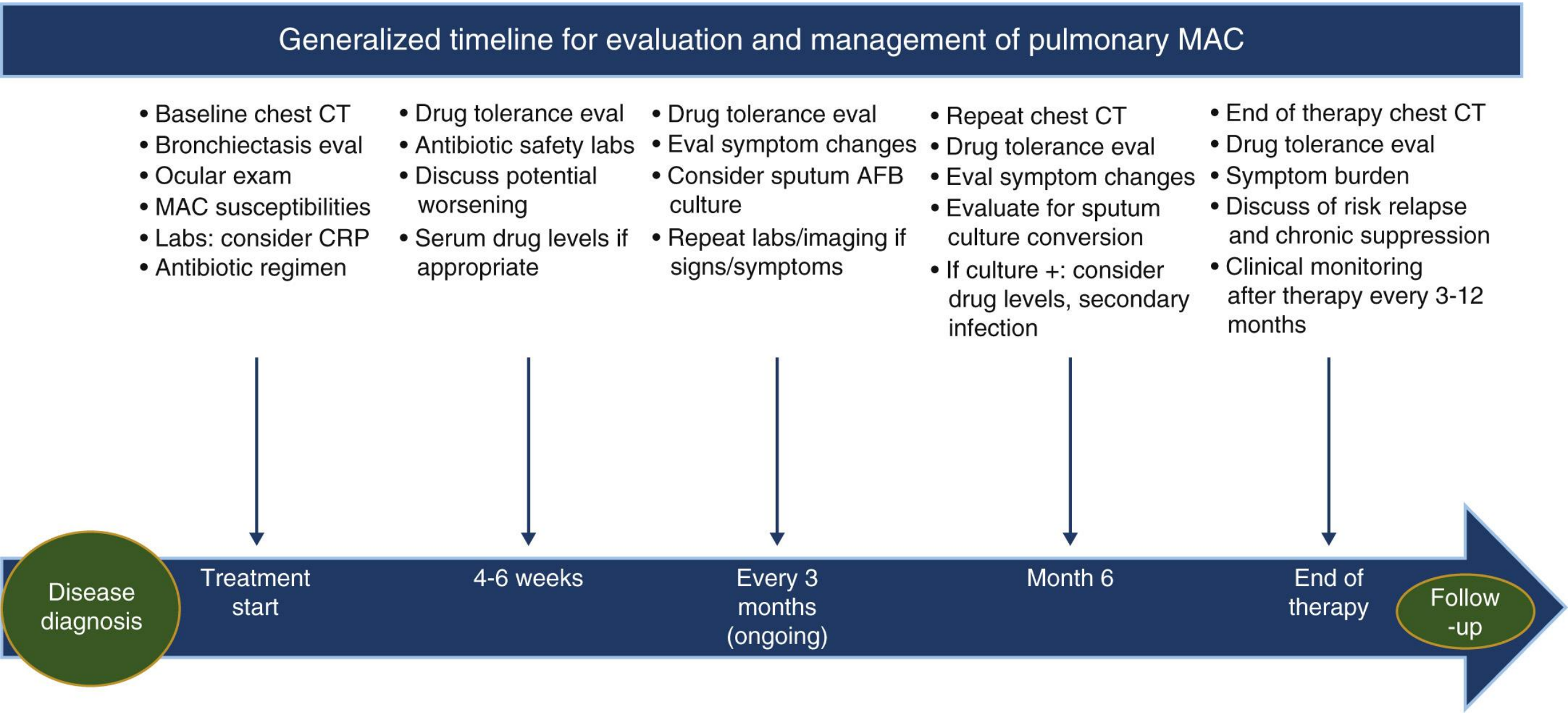
Duration of therapy – one year after culture conversion

Azithromycin > Clarithromycin

- Daily vs BID dosing
- Better tissue penetration
- Fewer side effects
- Fewer drug interactions
- Less metabolism by rifamycins

Van Ingen AJRCCM 2012
Haworth Thorax 2017
Daley CID 2020

Generalized timeline for evaluation and management of pulmonary MAC



Strnad LC Manell, Douglas and Bennett's Principles and Practice of Infectious Diseases

Important and/or common toxicities

Macrolides*	Rifamycins	Ethambutol	Aminoglycosides
• GI • Taste disturbance • QT prolongation • Drug interactions • Tinnitus, hearing loss	• Orange urine, tears • Hepatitis • Hypersensitivity syndromes • Leukopenia • Drug interactions	• Optic neuritis • Peripheral neuropathy	• Ototoxicity • Nephrotoxicity • Bronchospasm, dysphonia (if inhaled)

*all tend to be worse with clarithromycin than azithromycin

Patient education: medication side effects

https://www.youtube.com/watch?v=3sVHodFi8gY

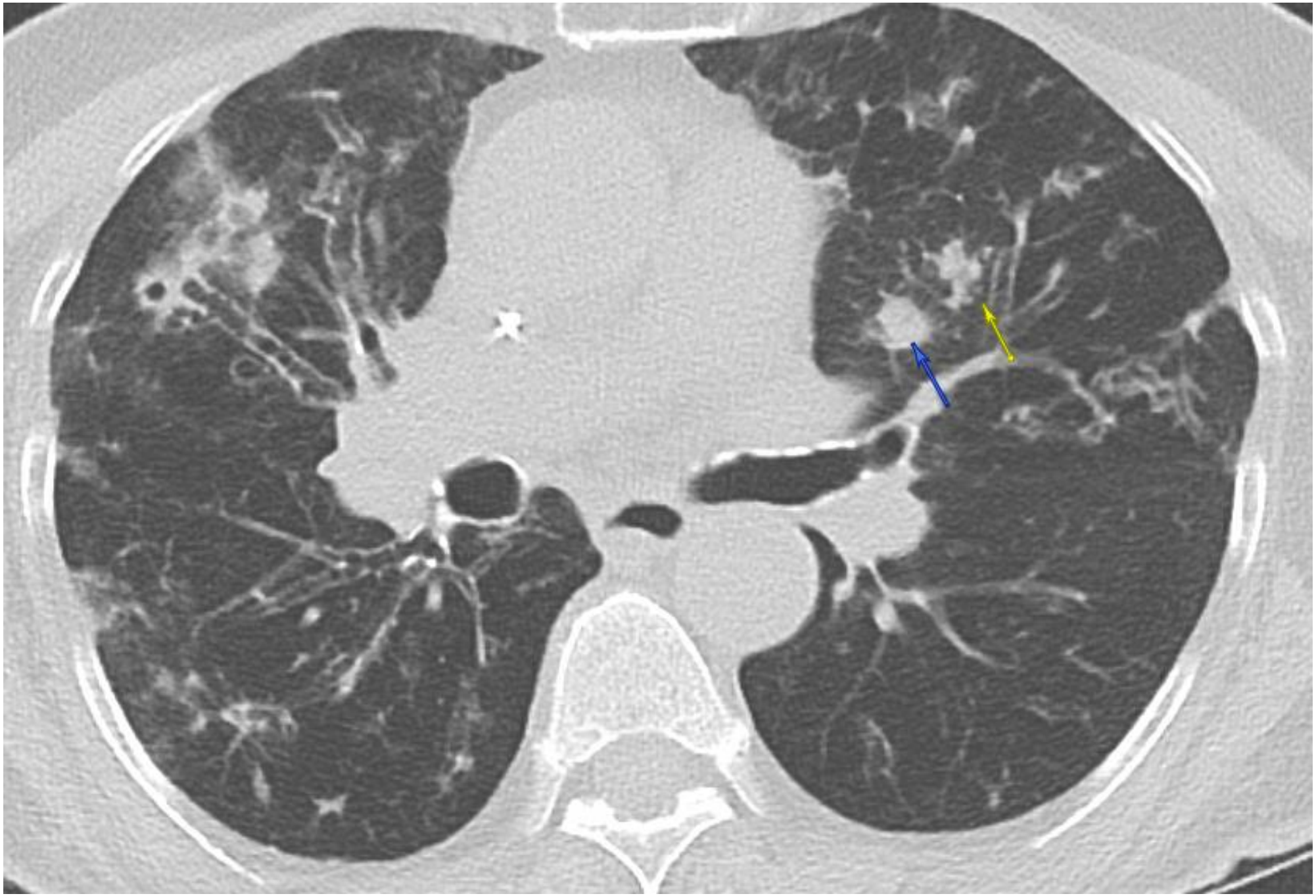
Do not use macrolide monotherapy!

- Rationale
  - Macrolide monotherapy or macrolide plus quinolone: 20% resistance
  - Macrolide plus ethambutol and rifampin: 4% resistance
- Strong correlation between macrolide resistance, persistently positive cultures, treatment failure, and mortality
- Recall: treat bronchiectasis flares with antibiotics NOT used for NTMs

Griffith D, et al. Am J Respir Crit Care Med 2006;174(8):928-34.

Case Presentation

- 83-year-old woman referred for consideration of NTM treatment
- Lengthy history of recurrent pulmonary infections dating to childhood, including a prolonged hospitalization for pneumonia at age 18, and another at age 60; always thin and “fragile”
- Depression (on citalopram); sensitive stomach
- Moderate-severe bronchiectasis on imaging; multiple consolidative nodules
- Over past year, weight down from 110 to 105 lbs
- 2/2 sputum samples positive for *M abscessus* subspecies *abscessus*

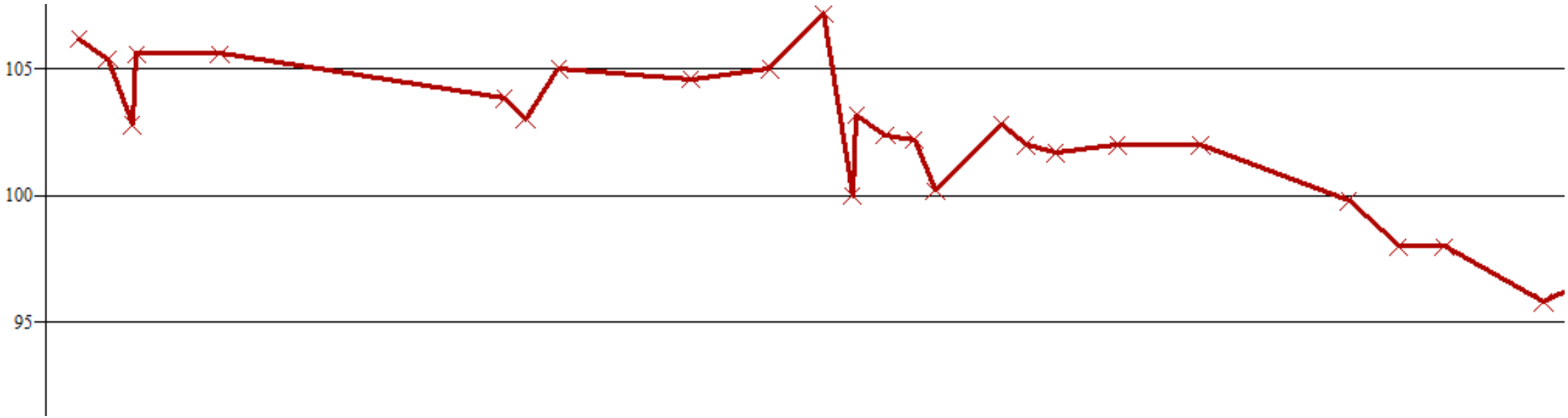


SUSCEPTIBILITY PATTERN OF: *Mycobacterium abscessus complex*

	S = SUSCEPTIBLE	R = RESISTANT	I = INTERMEDIATE	
ANTIBIOTICS	Microdilution MIC (µg / mL)	S	I	R
TMP-SMX	4/76			✓
Linezolid	8	✓		
Ciprofloxacin	4			✓
Imipenem	32			✓
Moxifloxacin[1]	4			✓
Cefoxitin	32		✓	
Amikacin	8	✓		
Doxycycline	>16			✓
Minocycline	>8			✓
Tigecycline[2]	0.12			
Tobramycin	-			
Clarithromycin[3]	16			✓
Ertapenem[4]	-			
Meropenem[1]	-			
Clofazimine[2]	-			

COMMENTS: Clarithromycin resistance due to inducible erm gene

Weight graph over time

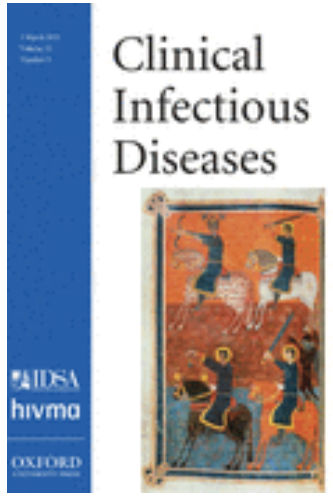


Case Presentation

- Patient informed that treatment was unlikely to be curative, and associated with many side effects – she elects to be monitored
- 6 months later, she reconsiders
- Admitted to hospital and started on imipenem, amikacin, linezolid, and azithromycin; citalopram d/c'd
- Course notable for SSRI withdrawal (linezolid → tedizolid), amikacin-induced increased creatinine, oral thrush, and further weight loss
- Oral therapy of tedizolid, azithromycin, and clofazimine continued for 4 months after initial 1 month IV course – ultimately stopped due to side effects
- Gradual decline in exercise capacity, functional status, weight continue

M abscessus spp pulmonary infection

- Organism has extensive drug resistance
  - Subspecies *M abscessus* and *M bolletii* intrinsically resistant to macrolides due to inducible erm41 gene; not present in *M massiliense*
- Medical treatment complex and rarely curative
  - Typical regimen starts with two parenteral agents for 8 weeks, e.g., imipenem or cefoxitin plus amikacin, with additional oral agents (linezolid, azithromycin, clofazimine) – oral regimen alone continued thereafter
- Consultation with thoracic surgery for localized disease – best chance at cure



Griffith DE. Clin Infect Dis 2011;52:572-4.

Treatment and Outcomes differ by species

NTM	Drugs	Duration	Expected Cure
M kansasii	INH or macrolide Ethambutol Rifampin	>12 months	95%
M avium complex	Macrolide Ethambutol Rifampin	>12 months	56%-85%, depends on extent of disease and macrolide susceptibility; 30% relapse
M abscessus group	Macrolide Imipenem Amikacin Other oral agents (?)	As long as tolerated	25% if macrolide resistant, up to 80% if sensitive

Additional Therapies for NTM Pulmonary Disease

- Inhaled liposomal amikacin (if S- amikacin)
- Bedaquiline
- Linezolid and tedizolid
- Clofazimine
- Meropenem-vaborbactam
- Omadacycline

Olivier KN, et al. Am J Respir Crit Care Med. 2017;195:814-823. Yagi K, et al BMC Infect Dis 2017 Aug 9;17(1):558. Vesenbeckh S, et al. European Respiratory Journal 2017; Winthrop KL, et al Eur Respir J. 2015;45:1177-1179. Martiniano SL et al. Chest 2017;152:800-809; Philley JV, et al. Chest. 2015;148:499-506. Pearson J, et al. Open Forum Infect Dis 2020.

Bacteriophages on the horizon

Open Forum Infectious Diseases

BRIEF REPORT

Nebulized Bacteriophage in a Patient With Refractory *Mycobacterium abscessus* Lung Disease

Rebekah M. Dedrick,[1,a] Krista G. Freeman,[1,a] Jan A. Nguyen,[2,a] Asli Bahadirli-Talbott,[2] Mitchell E. Cardin,[2] Madison Cristinziano,[1] Bailey E. Smith,[1] Soowan Jeong,[2] Elisa H. Ignatius,[3,4] Ch

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Phage Therapy of *Mycobacterium* Infections: Compassionate-use of Phages in Twenty Patients with Drug-Resistant Mycobacterial Disease

Rebekah M. Dedrick, Bailey E. Smith, Madison Cristinziano, Krista G. Freeman, Deborah Jacobs-Sera, Yvonne Belessis, A. Whitney Brown, Keira A. Cohen, Rebecca M. Davidson, David van Duin ... Show more

Author Notes

Clinical Infectious Diseases, ciac453, https://doi.org/10.1093/cid/ciac453

Published: 09 June 2022 **Article history** ▾

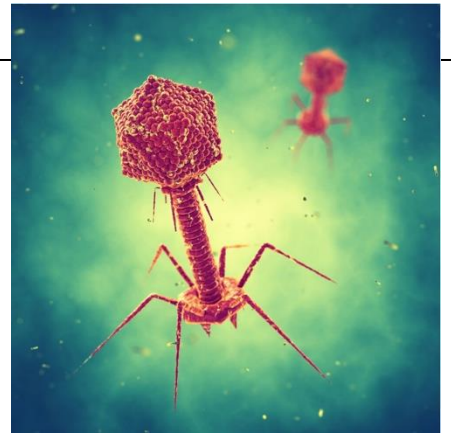
Cell

Volume 185, Issue 11, 26 May 2022, Pages 1860-1874.e12

Article

Host and pathogen response to bacteriophage engineered against *Mycobacterium abscessus* lung infection

Jerry A. Nick [1, 2, 9], Rebekah M. Dedrick [3], Alice L. Gray [2], Eszter K. Vladar [2], Bailey E. Smith [3], Krista G. Freeman [3], Kenneth C. Malcolm [1], L. Elaine Epperson [4], Nabeeh A. Hasan [4], Jo Hendrix [4, 5], Kimberly Callahan [4], Kendra Walton [4], Brian Vestal [4], Emily Wheeler [1], Noel M. Rysavy [1], Katie Poch [1], Silvia Caceres [1], Valerie K. Lovell [1] ... Rebecca M. Davidson [4]



Patient education is vital! Reassure but temper expectations carefully

- Reassure that they are not contagious to others
- Stopping even one drug could risk treatment failure, resistance
- Drug toxicities are common, but can be managed with staggered start, dose-adjustments, other strategies
- Clinical improvement may take several weeks
- Monitoring is critical – weight, blood tests (CBC, metabolic panel), sputum assessments (every 1-2 months until negative), eye exams (every 3-6 months while on ethambutol)
- F/u imaging should be deferred until end of treatment or for clinical relapse – do not expect all abnormalities to resolve
- Treatment is not a lifetime cure – reinfection may occur

Patient counseling about prevention of exposure and disease progression

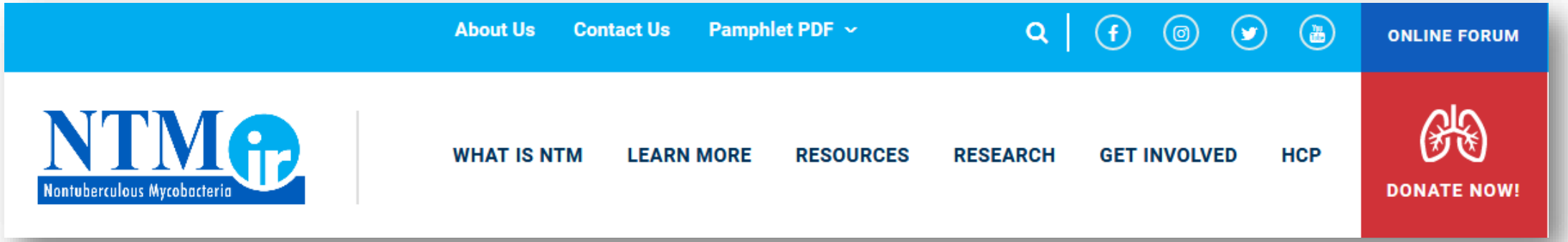
- Use showerhead with large diameter stream
- Maintain water in hot water heater > 130F
- Avoid hot tubs, spas, especially indoors
- Use distilled water in humidifiers and CPAP machines
- Get evaluated and treated for GERD
- Head of bed elevated while sleeping
- Mask while gardening
- ***Airway clearance strategies – here's where you can help us!***

IMPACT™
Individual Management of Patient Airway Clearance Therapy

https://impact-be.com/

Falkinham JO, et al. Semin Respir Crit Care Med. 2013;34:95-102.

NTMInfo.org: Useful resource for patients and their families



NTM Pulmonary Disease – Much Still to Learn, With Many Unanswered Questions!

- Who are the best candidates for treatment?
- Would treatment of mild disease prevent later complications, or just expose patient to drug toxicity and select for resistance?
- What is the optimal frequency of imaging?
- What is the best way to prevent disease?
- What are the most effective and safest regimens?
- Does NTM cause low BMI, or is a low BMI somehow predisposing to NTM?
- Who should undergo genetic testing?
- Who should be referred for surgery?
- *How can Pulmonary and ID best collaborate on these challenging cases?*

Pulmonary NTM disease – Take-home points

- Suspect pulmonary NTM in any patient with chronic, recurrent symptoms unresponsive to short courses of antibiotics
  - Be *especially* suspicious in susceptible hosts (bronchiectasis, women with low BMI, COPD, CF)
  - Watch out for TNF-blockers
- Confirm diagnosis by incorporating clinical and microbiologic data – no rush to treat
- Prolonged combination therapy – avoid macrolide monotherapy
- *Team approach* with your ID friends and colleagues