Nontuberculous Mycobacterial Lung Disease – Challenges in Diagnosis and Treatment

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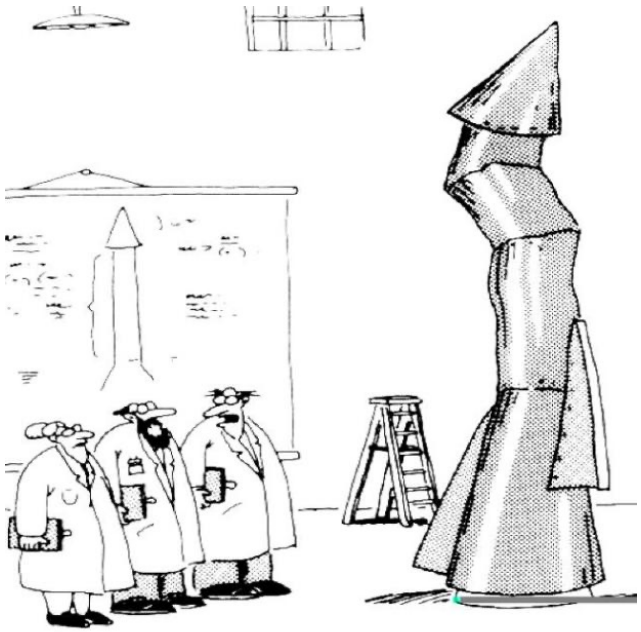
Disclosures

- None

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
- Guidelines outdated
- Classic “hot potato”!



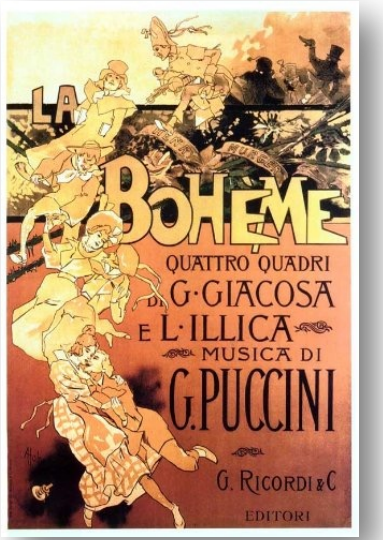
“It’s time to face reality, my friends... We’re not exactly rocket scientists.”

Goals of this presentation

- Decrease confusion about pulmonary NTMs, especially microbiology and susceptibility testing
- Provide an approach to diagnosis and treatment
- Present some relevant cases
- Put in a pitch for advocacy

NTMs: Defined by what they are not!

- Considered not NTMs
  - *Mycobacterium tuberculosis*
  - *Mycobacterium leprae*



- NTMs – *all* the rest, approximately 200 species! Previously "MOTT"
- 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.

Some slow vs. “rapid” growers

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

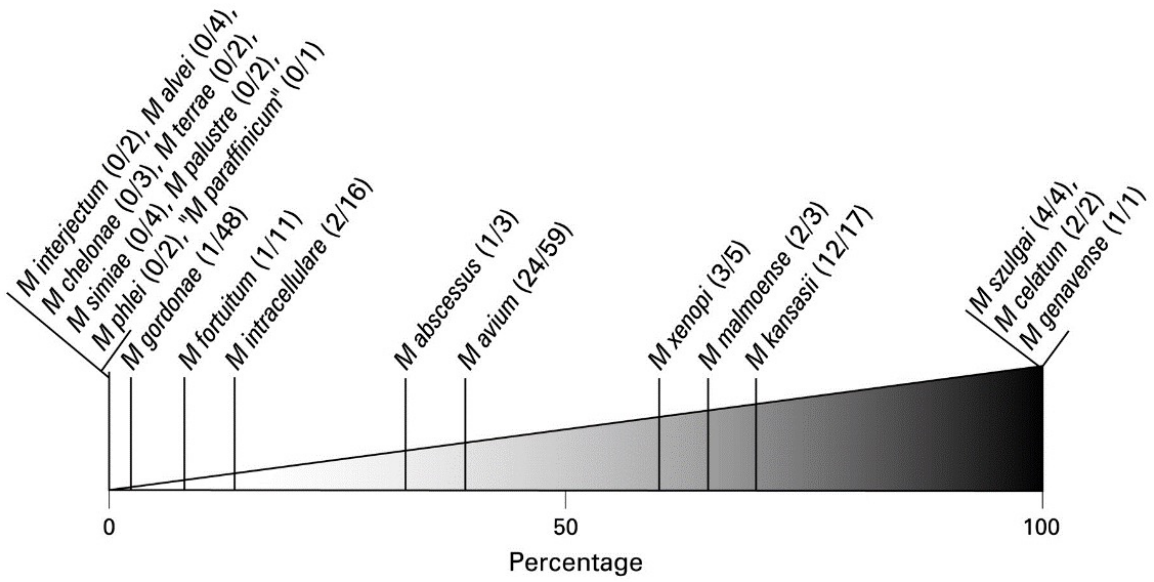
- Rapid growers*
  - ***M abscessus* group**
    - *M abscessus*
    - *M boleti*
    - *M massilience*
  - *M fortuitum*
  - *M chelonei*

*Grows in culture by 7 days

Respiratory infection

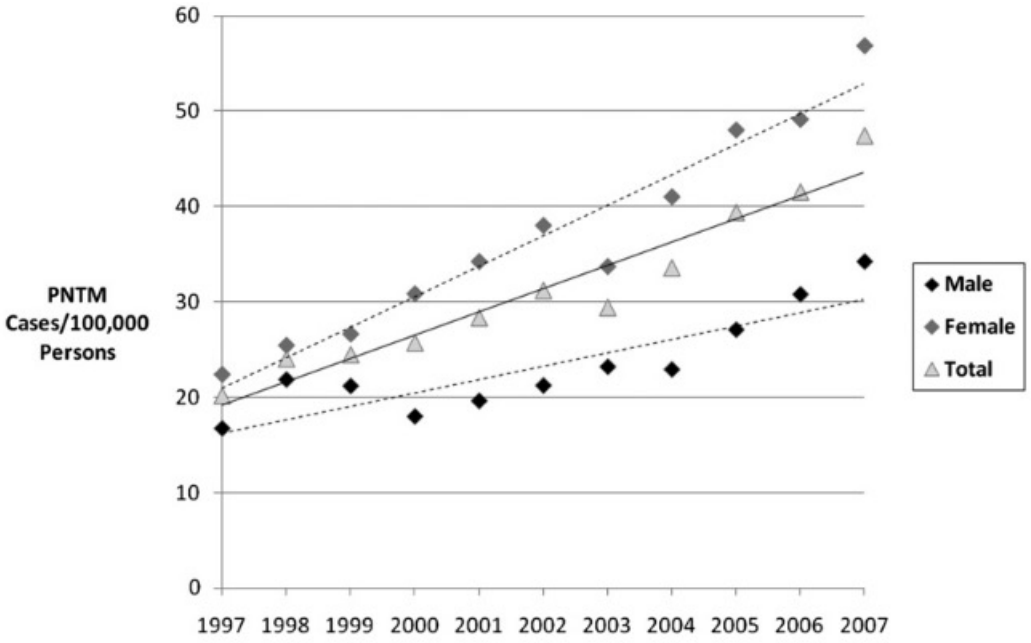
Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, The Netherlands FREE

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]

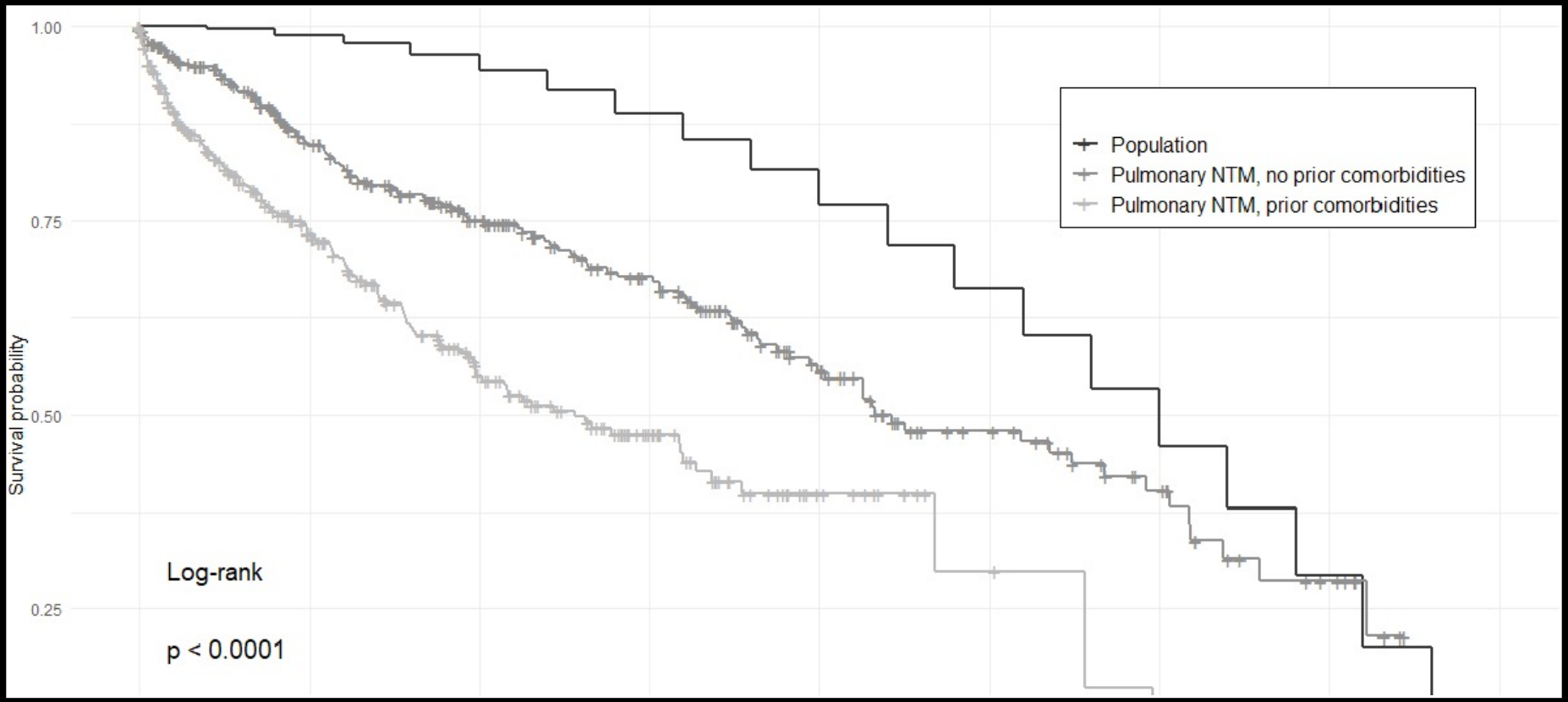


Thorax 2009;64:502-506

NTM pulmonary infections are increasing



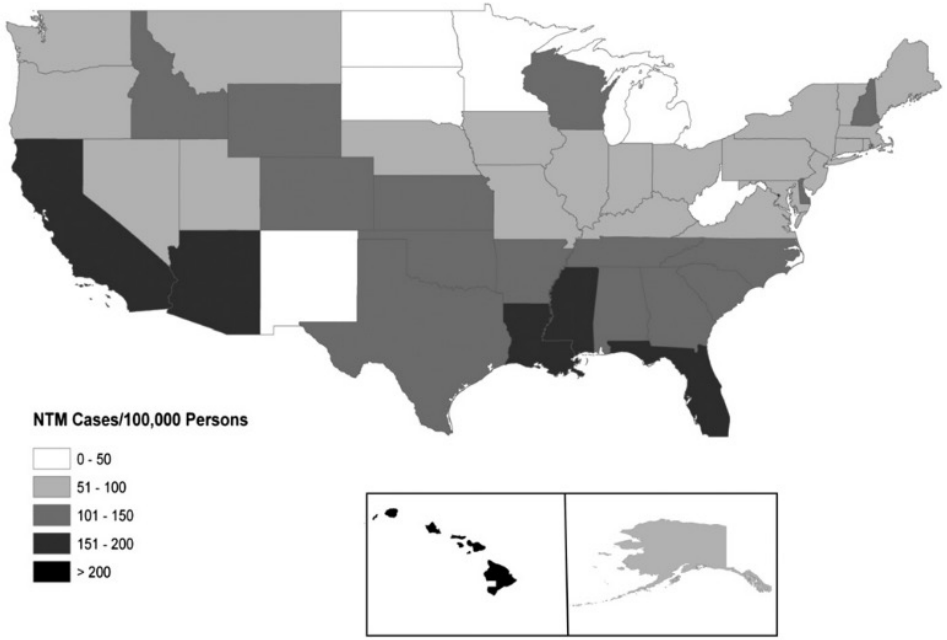
Adjemian J, et al. Am J Respir Crit Care Med. 2012;185:881-886.



Diagnosis of NTM pulmonary disease associated with reduced survival

Mourad A, et al Clinical Infectious Diseases 2020.

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



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

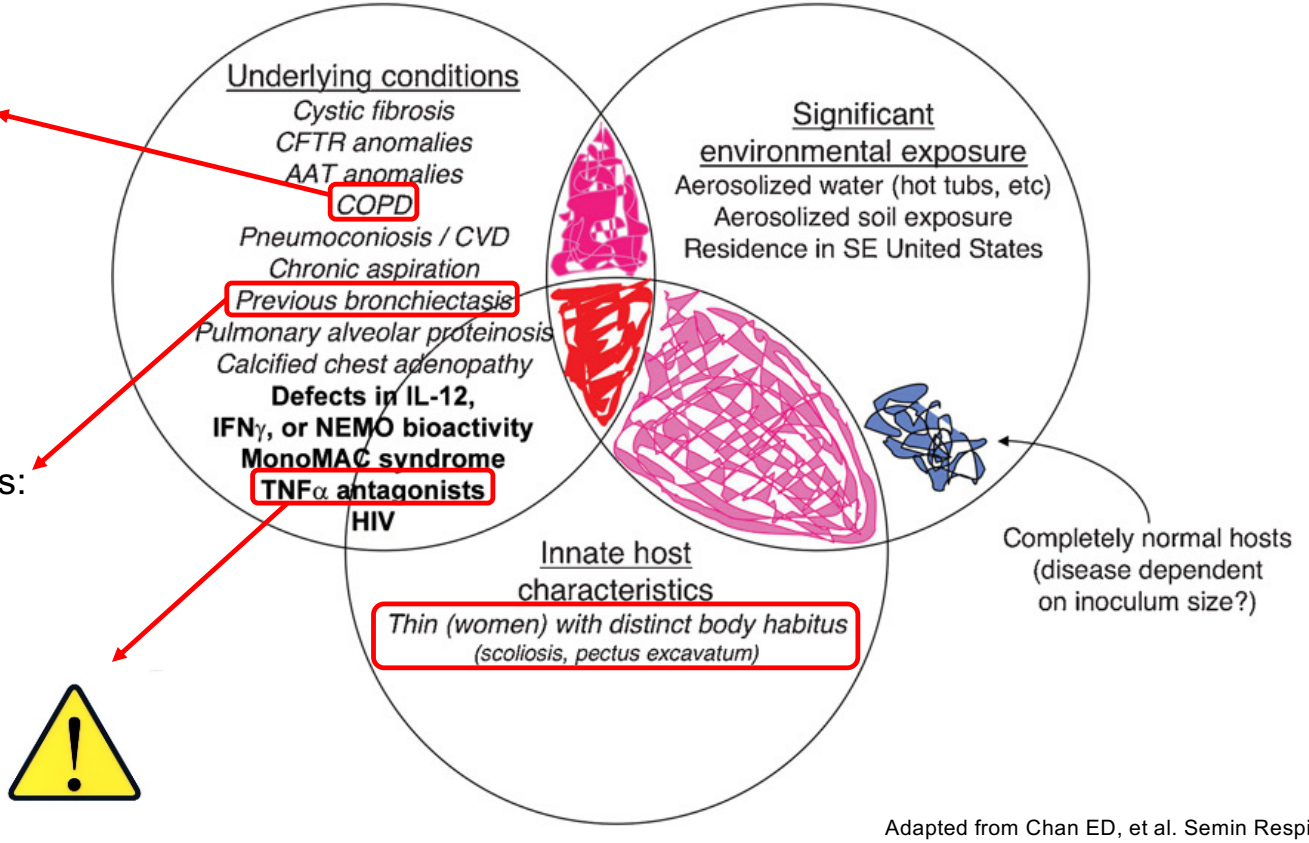
How do patients acquire pulmonary NTM?

- 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
- These sources provide some basis for counseling about prevention

Risk Factors for NTM Infections

COPD:
2-10X

Bronchiectasis:
44-188X



Adapted from Chan ED, et al. Semin Respir Crit Care Med 2013; 34(01): 110-123.

NTM Pulmonary Disease and Excess Mortality

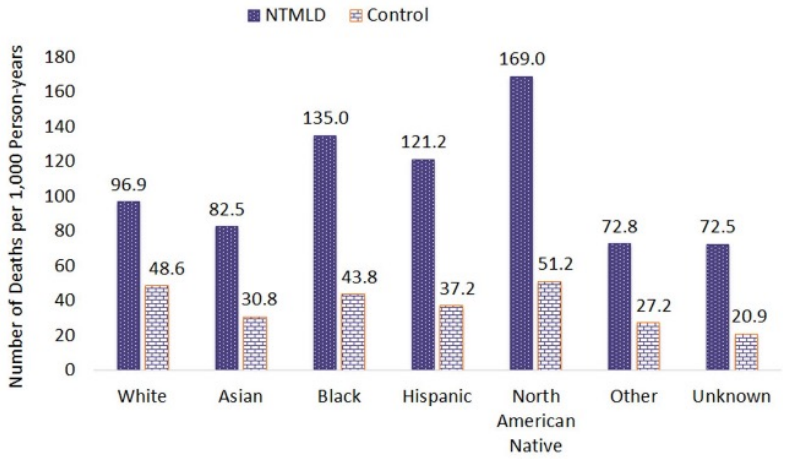
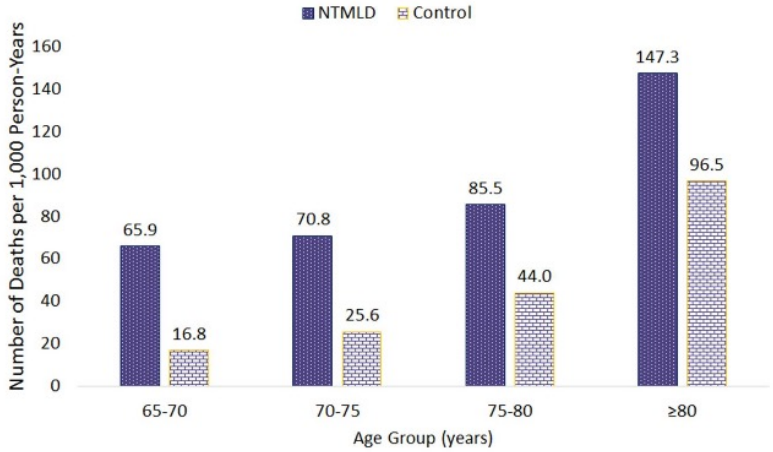


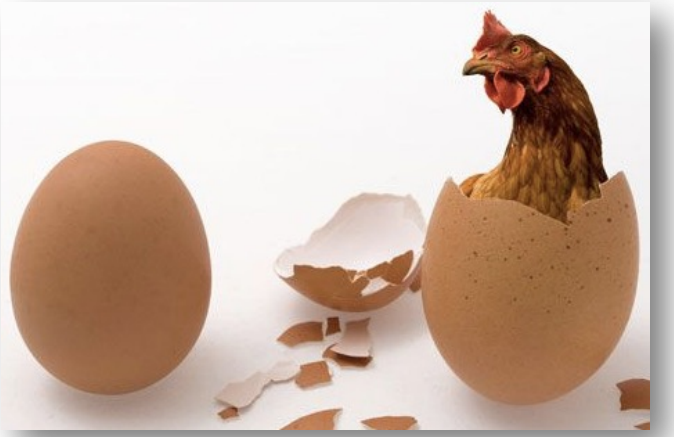
Figure 1: Observed Mortality by Race Groups



Marras T, et al. IDWeek 2018, San Francisco. Abstract #122.

Pulmonary NTMs: When to consider the diagnosis

- *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!
- Bronchiectasis on imaging

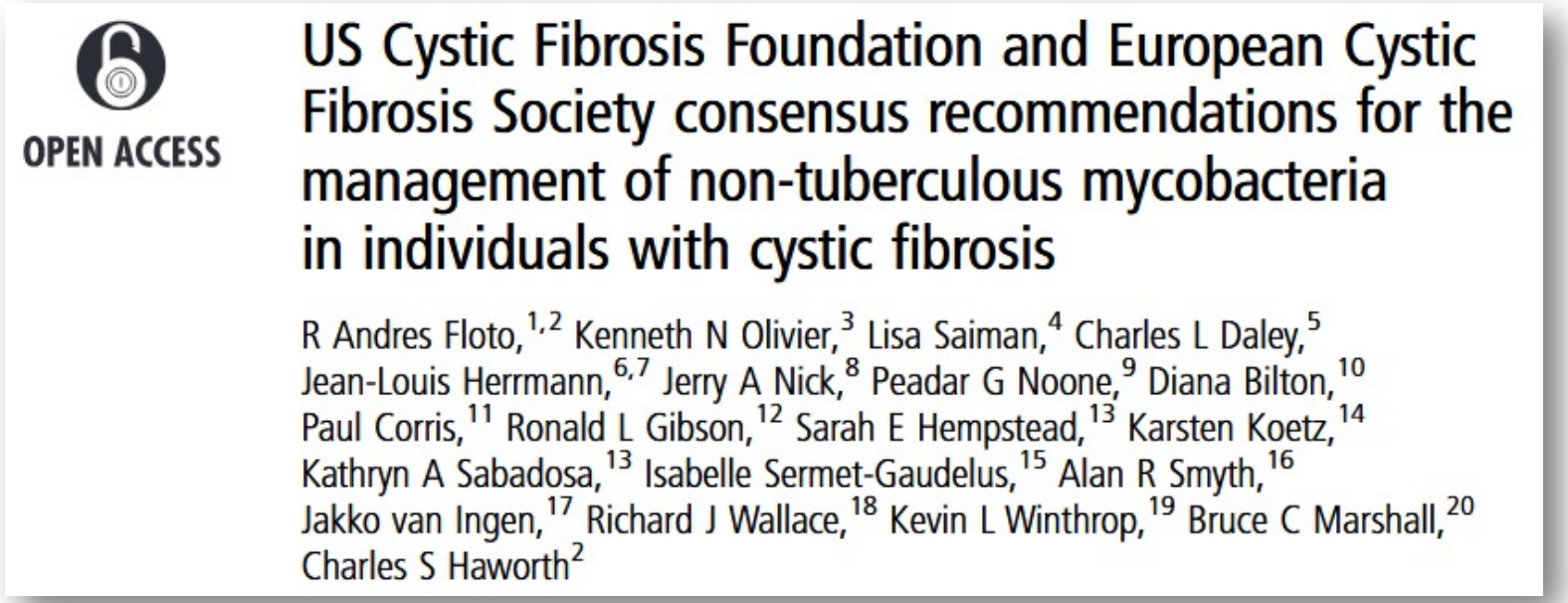


Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

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.

Also useful – even for non-CF cases



OPEN ACCESS

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

R Andres Floto,[1,2] Kenneth N Olivier,[3] Lisa Saiman,[4] Charles L Daley,[5] Jean-Louis Herrmann,[6,7] Jerry A Nick,[8] Peadar G Noone,[9] Diana Bilton,[10] Paul Corris,[11] Ronald L Gibson,[12] Sarah E Hempstead,[13] Karsten Koetz,[14] Kathryn A Sabadosa,[13] Isabelle Sermet-Gaudelus,[15] Alan R Smyth,[16] Jakko van Ingen,[17] Richard J Wallace,[18] Kevin L Winthrop,[19] Bruce C Marshall,[20] Charles S Haworth[2]

Floto RA,et al.Thorax 2016;71:i1–i22.

Clinical and microbiologic criteria for diagnosis of NTM disease

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results 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 one or more sputum or bronchial washings that are culture positive for NTM	

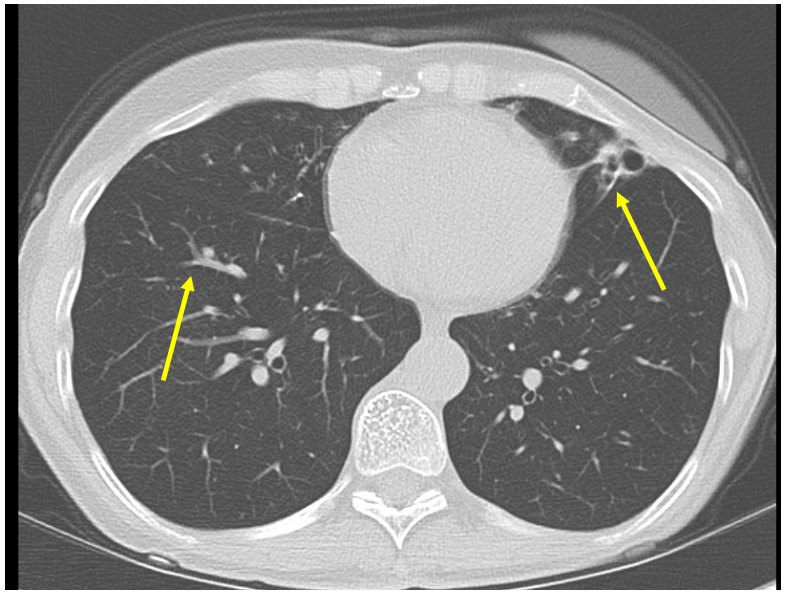
Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.

Case presentation

- 61-year-old woman, longstanding subjectively poor exercise tolerance compared to her very fit friends
- Became more noticeable during biking trip in Florida – returned home to Boston and saw PCP
- PMHx: Frequent episodes of “bronchitis”, requires antibiotics several times a year with marked GI side effects; always very thin despite good appetite, has many jealous friends
- SHx: Smoked briefly in her 20s; avid gardener
- PE notable for O2 sat 98%, weight 104 lbs, BMI 18.4 (stable)

Case presentation

- PFTs normal; CXR with scoliosis and possible pulmonary nodule
- CT: clusters of inflammatory-appearing nodules, “tree-in-bud” opacities; mild cylindrical bronchiectasis
- Undergoes induced sputum exams on 3 separate days
- All are smear-negative for mycobacteria; 2/3 are culture positive for *Mycobacterium avium* complex (MAC)



Question

?

- What would you do now?

A. Collect more information prior to discussing benefits vs risks of treatment
B. Start multi-drug therapy now for MAC for 12-18 months
C. Treat for bronchitis with standard antibiotics for 7-14 days
D. Not sure

Does our case have pulmonary NTM? *Yes!*

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

- *However, 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.*

Treatment vs observation ("watchful waiting") in latest guidelines

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.

BUT:

No randomized, controlled trials have been conducted to examine the impact of treatment on either survival or quality of life. Limited retrospective observational data have failed to demonstrate that treatment of NTM pulmonary disease prolongs survival over watchful waiting.

AND:

Importantly, just because a patient meets diagnostic criteria for NTM pulmonary disease does not necessarily mean antibiotic treatment is required.

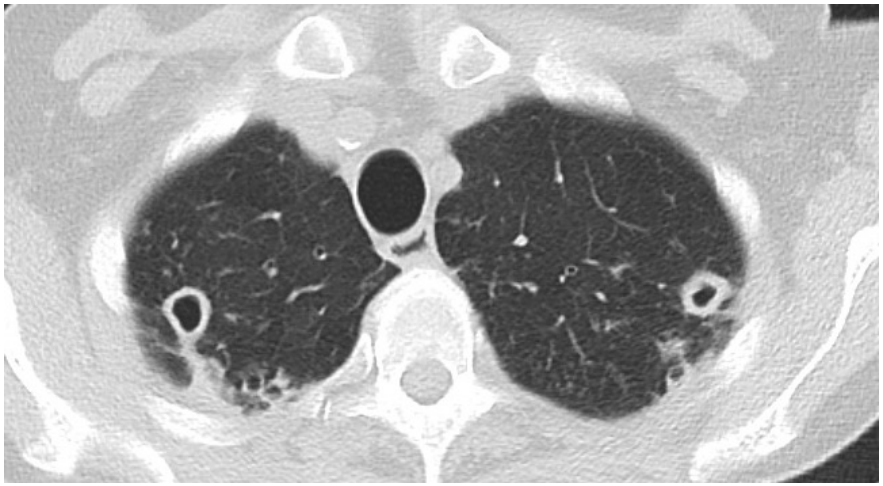
Daley CL, et al. Clinical Infectious Diseases 2020, Pages e1–e36.

Case presentation

- 68-year-old woman with cough, night sweats, and weight loss
- PMHx: Treated for pulmonary TB as young adult while living in China; smoked 1 ppd cigarettes for 40 years; moved to USA in 2001 to be with her family
- Reports a month (“at least a year” says daughter, correcting her) of increased coughing over her baseline; also decreased appetite, night sweats, weight decreased from 110 to 102 lbs (BMI 17)
- Exam: Afebrile; coughing frequently

Case presentation

- CT chest – bilateral thin-walled cavities, multiple inflammatory-appearing nodules, moderate bronchiectasis
- Sputum evaluation – AFB smear positive, with negative GeneXpert for MTB
- Culture positive for "*MYCOBACTERIUM CHIMAERA INTRACELLULARE GROUP*"



Question ?

- After collecting all the primary data, what would you do now?

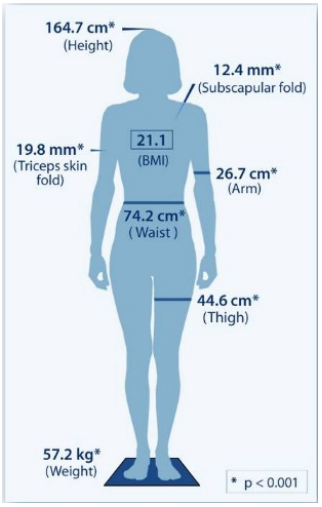
A. Treat with multi-drug therapy directed at MAC for 12-18 months
B. Treat with a multi-drug regimen directed at both MAC and TB for 12-18 months
C. Treat for bronchitis with standard antibiotics for 7-14 days
D. Not sure

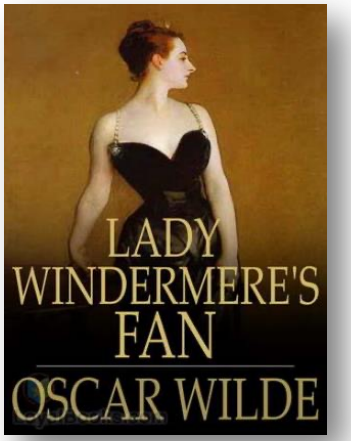
Radiologic patterns of pulmonary NTM disease

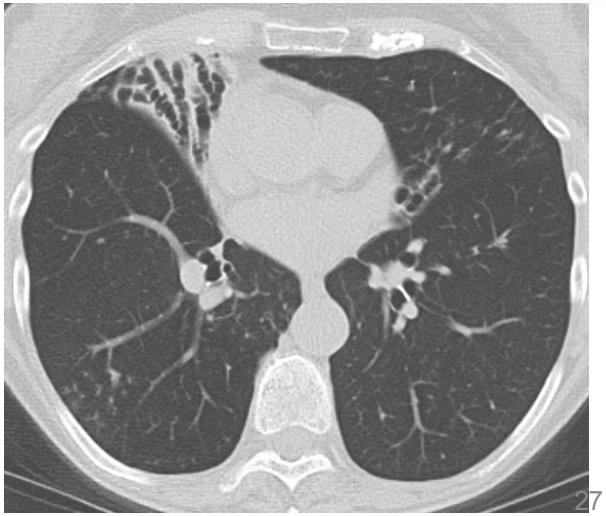
- Bronchiectasis
- Nodules
- Cavities
- Consolidation
- Two main forms of pulmonary NTM disease
  - Nodular bronchiectatis – thin women
  - Fibrocavitary – COPD is biggest risk, often high organism burden
  - Overlap is common, especially in severe and progressive bronchiectasis

Nodular bronchiectasis

- Thin, post-menopausal women
- Often non-smokers or ex-smokers
- Scoliosis, pectus excavatum significantly more common than in age-matched controls
- Slowly progressive
- Highly variable clinical presentation
- “Lady Windermere” – not really







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

Who should be treated?

- Base decision on symptoms, age, comorbidities, specific organism, drug susceptibilities – and ability to tolerate complex antimicrobial regimens
- *Favors observation*
  - Mild or intermittent symptoms, nodular bronchiectasis pattern on imaging
  - Re-evaluate in 6-12 months clinically and with CT scan – expect waxing and waning abnormalities
  - Aggressively treat bronchiectasis flares with antibiotics NOT used for NTMs (e.g., amox-clav, TMP/SMX, doxycycline)
- *Favors treatment*
  - Constitutional symptoms, especially weight loss and severe fatigue
  - Fibrocavitary disease, lung destruction
  - Smear positivity

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
- Request a *species-specific* diagnosis, especially for rapid growers
- 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!

	M. avium	
ANTIBIOTICS	MIC mcg/mL	INTRP
1_Rifampin (RIF)	1	TS
2_Ethambutol (EMB)	5	TI
3_EMB/RIF Combo Effect		ADD D1
4_Rifampin (Combo Assay)	0.5	TS
5_Ethambutol (Combo Assay)	2.5	TS
Amikacin	32	TR
Ciprofloxacin	>16	TR
Clarithromycin	4	TS
Clofazimine	<=0.12	TS
Linezolid	64	TR
Moxifloxacin	8	TR
Rifabutin	0.5	TI
Streptomycin	32	TR
x Compliance Statement		* D2
x Compliance Statement		* D3

S=Susceptible I=Intermediate R=Resistant NI=No CLSI interpretive guidelines for this antibiotic/organism combination.
TS=Tentative Interpretation Susceptible TI=Tentative Interpretation Intermediate TR=Tentative Interpretation Resistant

-----DRUG COMMENTS-----

D1 : ADD = Additive

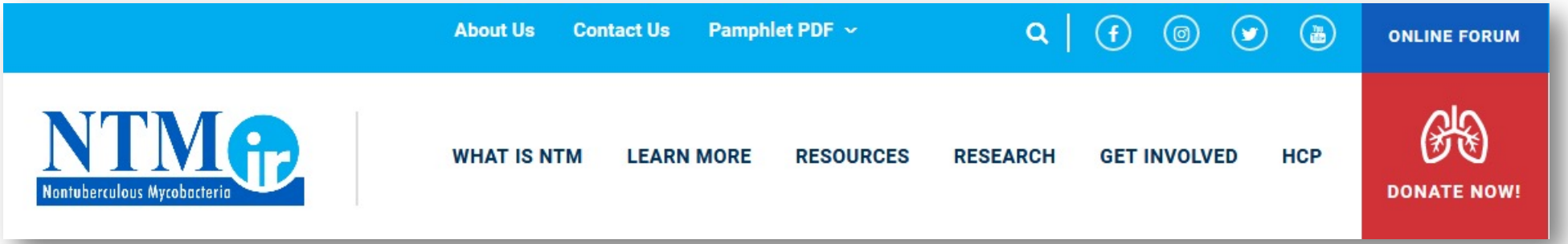
In the combination of Ethambutol + Rifampin, the effect is additive.

D2 : Testing was performed by the broth dilution microdilution method unless otherwise stated above. This assay is a laboratory developed test used for clinical purposes. It was developed and its performance characteristics determined by advanced diagnostic laboratories at National Jewish Health. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This assay was validated for M. avium complex only.

Patient education is vital! Reassure but temper expectations carefully

- Reassure that they are not contagious to others
- Mention that stopping even one drug could risk treatment failure, resistance
- Drug toxicities are common, but can be managed with staggered start, dose-adjustments, other strategies
- Educated that 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

NTMInfo.org: Useful resource for patients and their families



Treatment of macrolide-susceptible NTM lung disease due to MAC

- Stagger start to improve tolerability (3 days before adding next med)
- Mild nodular bronchiectasis – 3x/week treatment
  - Azithromcyin 500 mg (>>> clarithromycin 1000 mg), rifampin 600 mg, and ethambutol 25 mg/kg, all given once-daily 3X/week
- Severe nodular bronchiectasis or fibrocavitary disease – daily treatment
  - Azithromycin 250 mg (or clarithromycin 500 mg), rifampin 600 mg, ethambutol 15 mg/kg, all given once daily
  - Consider addition of amikacin 3X/week for at least 1 month
- Duration of therapy – one year after culture conversion

Clinical Infectious Diseases 2020, Pages e1–e36.

Do not use macrolide monotherapy!

- Rationale
  - Macrolide monotherapy or macrolide plus quinolone: 20% resistance
  - Macrolide plus ethambutol and rifampin: 4% resistance
- Similar data from studies in HIV with disseminated disease
- Strong correlation between macrolide resistance, persistently positive cultures, treatment failure, and mortality

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

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 counseling about prevention of exposure and disease progression

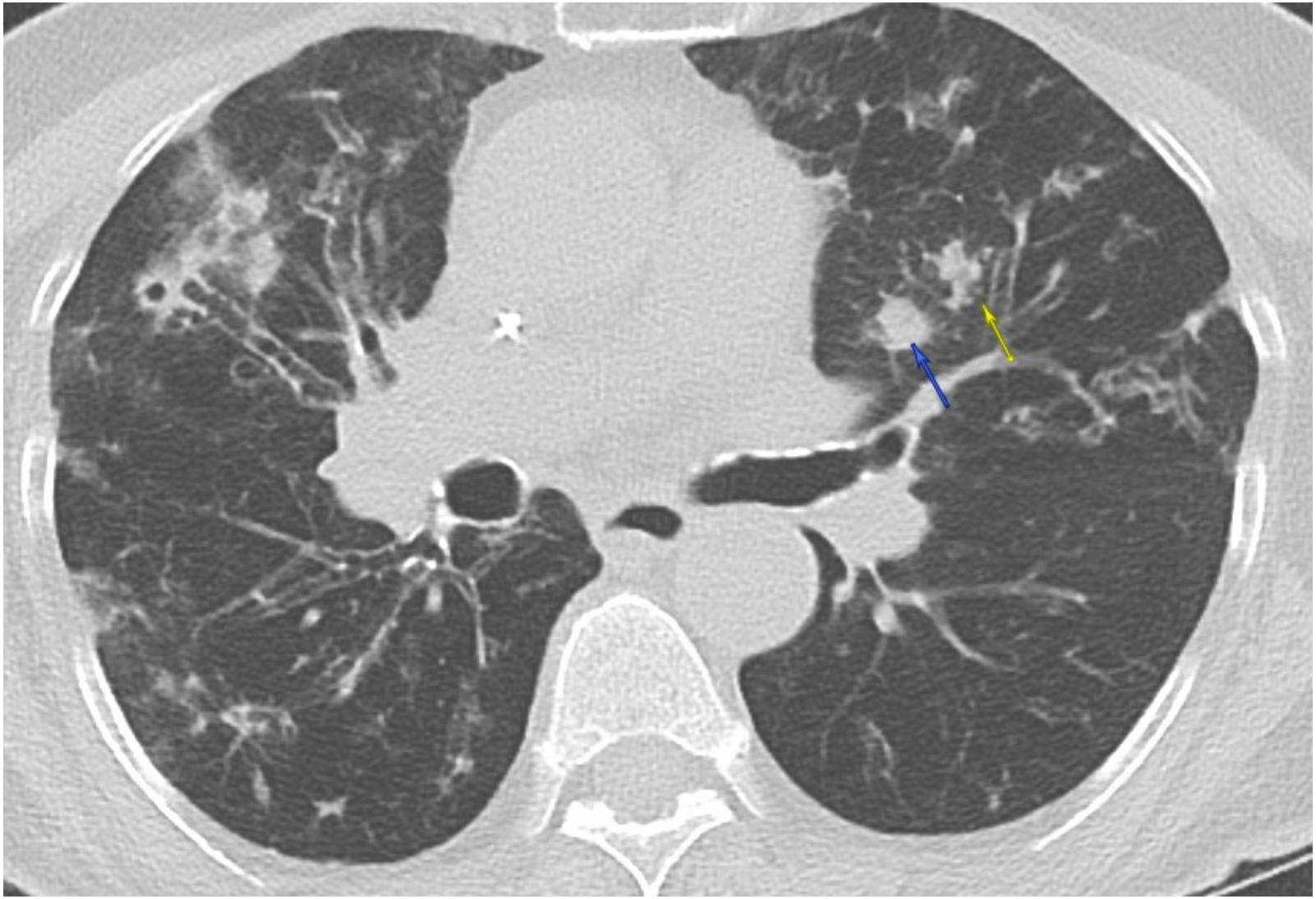
- Use showerhead with large diameter stream
- Use exhaust fan
- If water filter is used, must be < 0.45 micrometer
- Maintain water in hot water heater > 130F
- Avoid hot tubs, spas, especially indoors
- Use distilled water in humidifiers and CPAP machines
- Get evaluated and treated for GERD
- Head of bed elevated while sleeping
- Mask while gardening
- ***Airway clearance strategies – here's where you can help us!***

https://impact-be.com/

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

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*



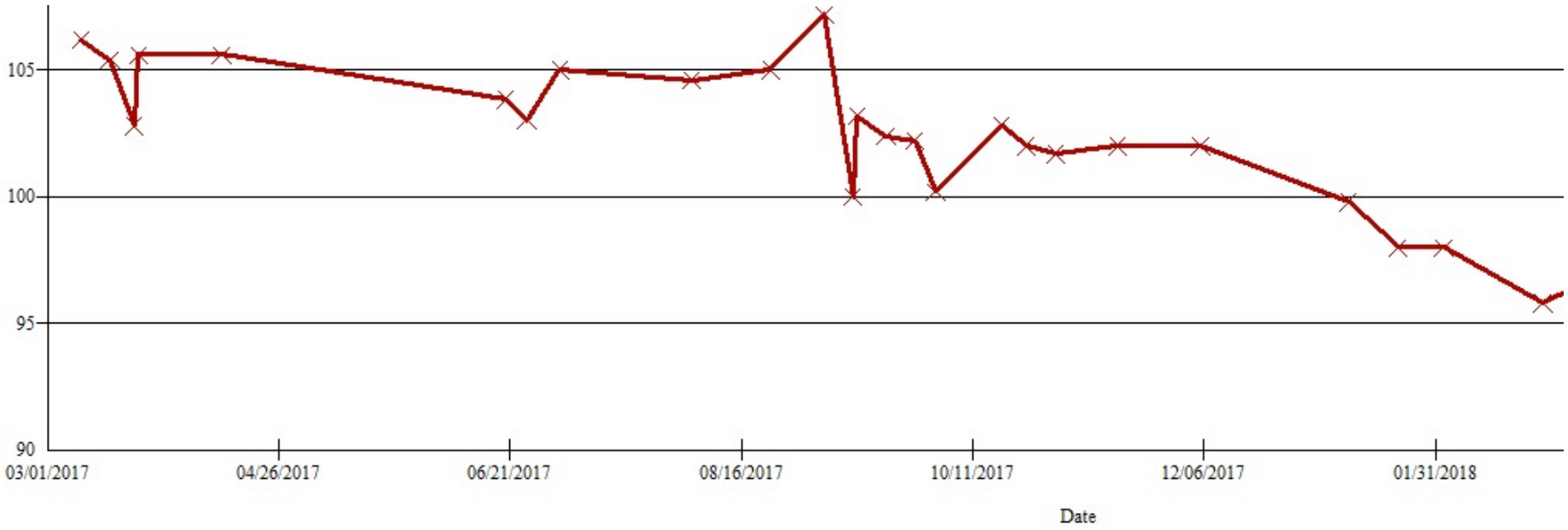
SUSCEPTIBILITY PATTERN OF: *Mycobacterium abscessus complex*

	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

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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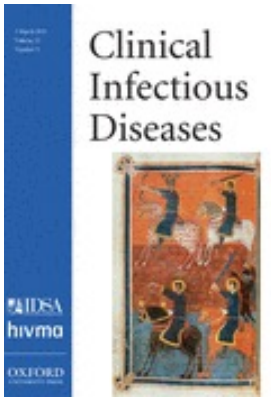
Date

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



"Sometimes it seems that the question is not why some people improve with current therapy for *M abscessus* disease, but rather, why does *anyone* improve with current therapy for *M abscessus* disease."

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

NTM Regimens and Outcomes

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 – FDA approved Oct 2018 for refractory MAC
  - Organism must be amikacin susceptible
- 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.

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 messages

- 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
- Combination therapy recommended – avoid macrolide monotherapy
- Treatment guidelines recently updated
- *Team approach* with your ID friends and colleagues