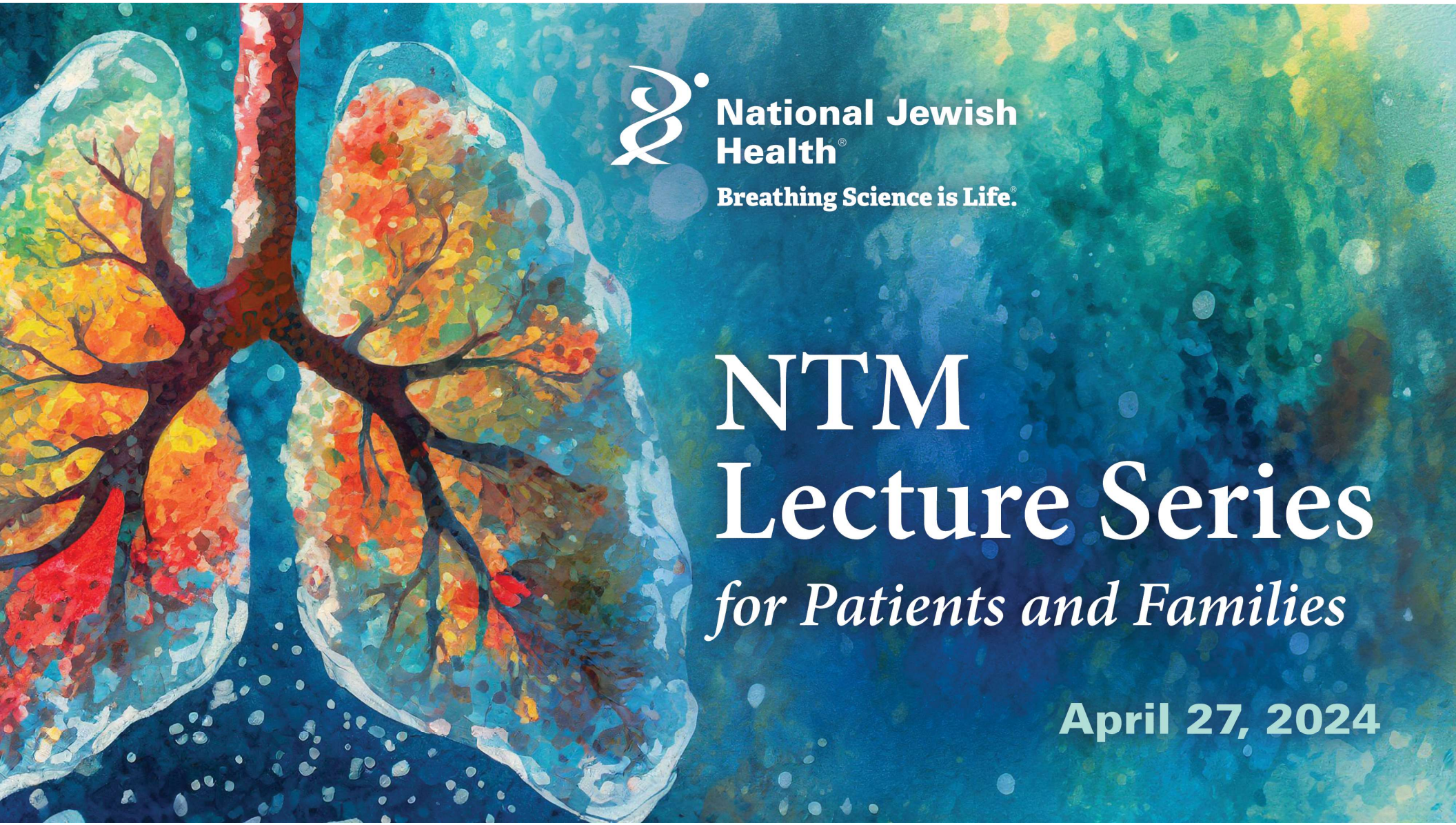
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NTM
Lecture Series
for Patients and Families
April 27, 2024

Treatment of Nontuberculous Mycobacterial (NTM) Infections

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National Jewish Health

National Jewish Health

Disclosures

Consultant: Genentech, Pfizer

Advisory Board Member: AN2, Hyfe, Insmed, MannKind, Matinas BioPharma Holdings, Inc., Nob Hill, Paratek Pharmaceuticals, Spero Therapeutics, Zambon

Data Monitoring Committee: Ostuka Pharmaceutical, Bill and Melinda Gates Foundation

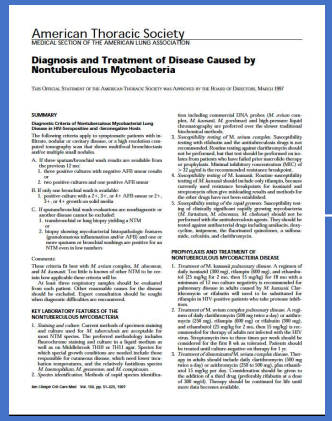
Contracted Research: AN2 Therapeutics, Bugworks, Insmed, Juvabis, Paratek Pharmaceuticals

NTM Treatment Guidelines

1990

DIAGNOSIS AND TREATMENT OF DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA

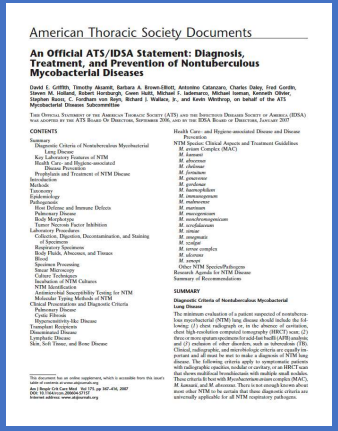
1997



American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria

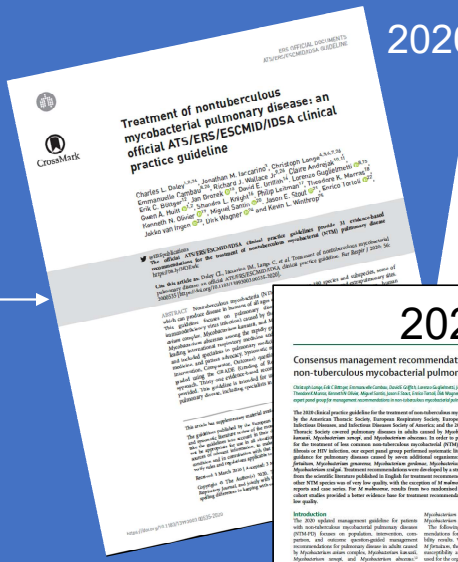
2007



American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

2020



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

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

2022

Review
Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535
Lange C, et al. Lancet Infect Dis 2022;22:e178-190

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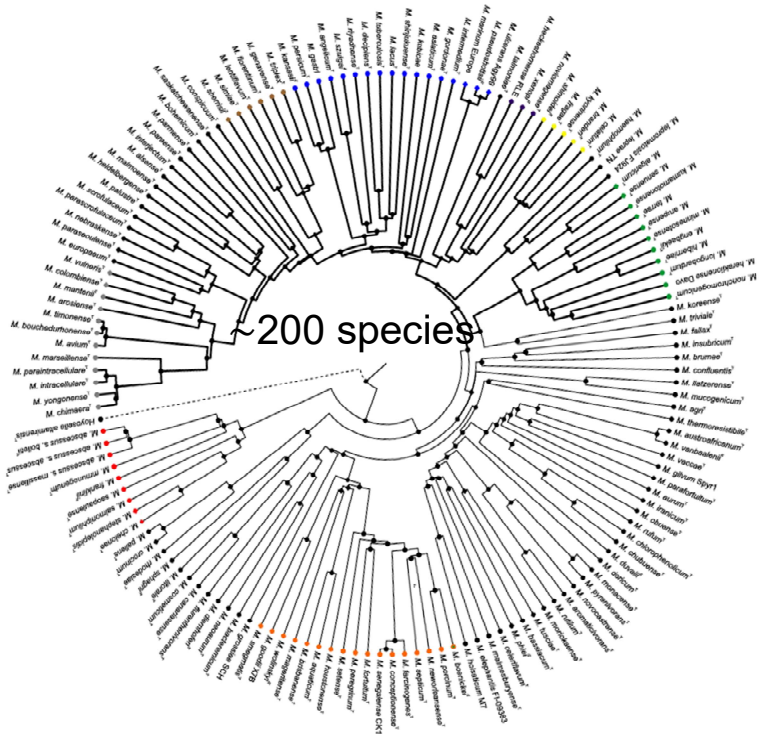
NTM Treatment Guidelines

<u>*Slow Growers*</u>
***M. avium* complex**
M. kansasii
M. Xenopi

<u>Rapid Growers</u>
M. abscessus



<u>*Slow Growers*</u>
M. malmoense
M. simiae
M. szulgai
M. genevense
M. gordonae

<u>*Rapid Growers*</u>
M. chelonae
M. fortuitum

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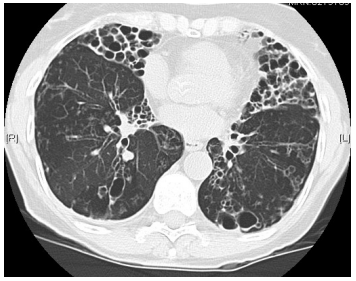
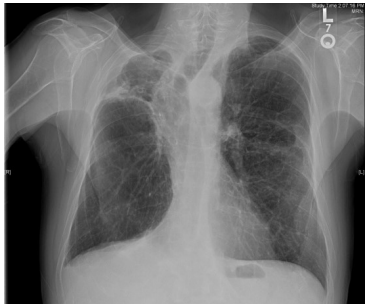
ATS Diagnostic Criteria For NTM Lung Disease

Clinical

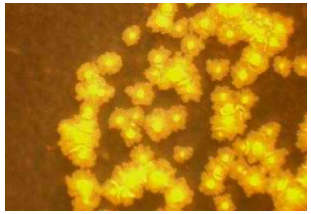
Cough
Fatigue
Weight Loss

Radiographs





Bacteriology



≥ 2 positive
sputum cultures

Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

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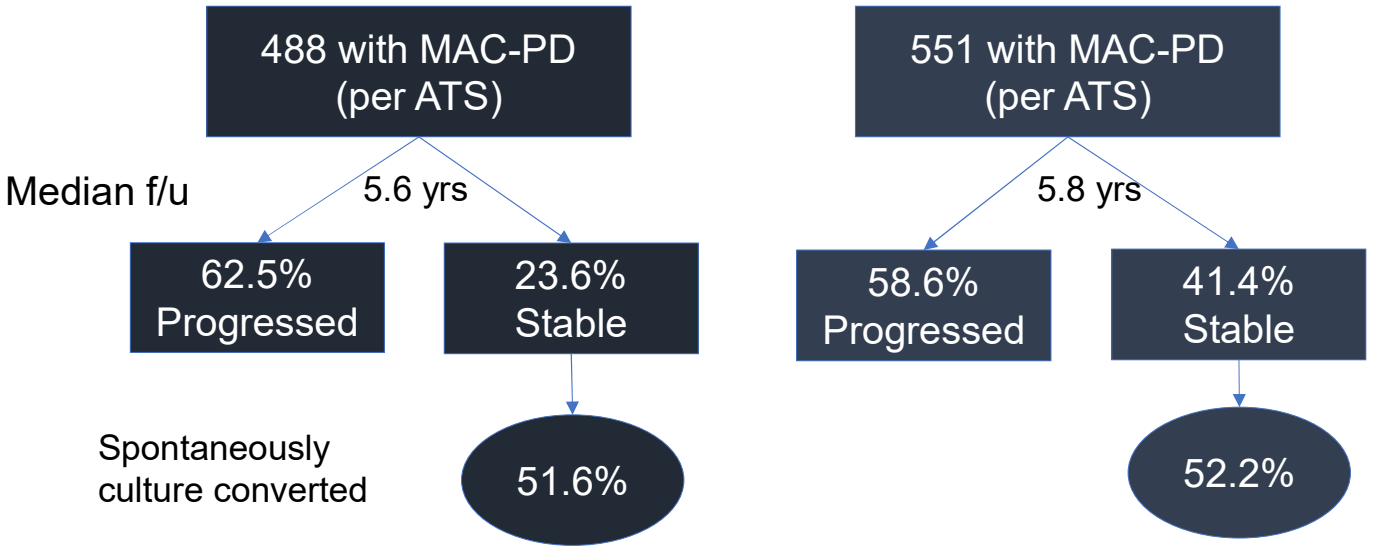
Watchful waiting or initiation of treatment?

Guideline 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).



Hwang JA, et al.
Eur Respir J 2017;49:1600537

Kwon BS, et al.
Resp Med 2019;150:45-50

Daley CL, et al. *CID* 2020;71:5-913; *Euro Respir J* 2020;56:2000535

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Whom to Treat?

Risk Factors Associated with Progression

Host/Demographic Factors

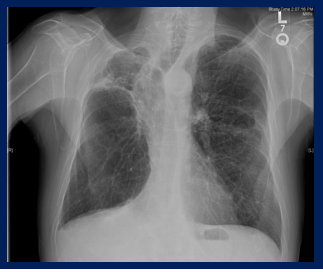
- Male gender
- Older age
- Presence of comorbidities
- Low body mass index

Laboratory Factors

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

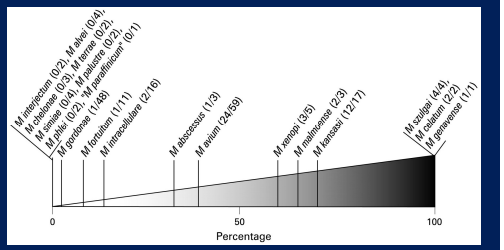
Radiographic Factors

- Fibrocavitary
- Extent of disease



Microbial Factors

- Bacterial load
- Species



Kwon BS et al. *Resp Med*. 2019;150:45-50.
Moon SM et al. *Resp Med*. 2019;151:1-7.

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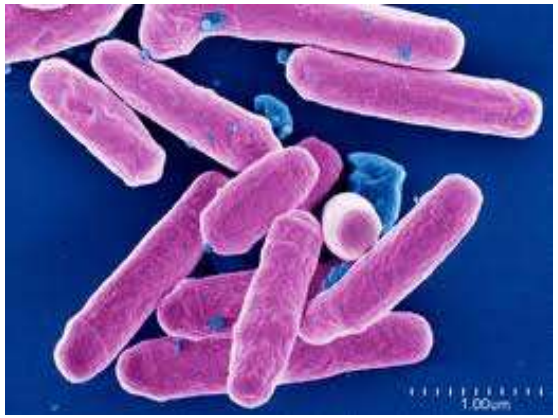
NTM Pulmonary Disease: Whom to Treat

Consider the:

Patient

Organism



Goals of Treatment

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NTM Pulmonary Disease: Whom to Treat

Patient

- Increased risk of progression?
  - Cavitation, positive AFB smear, other risk factors?
- Clinical symptoms and overall condition?
  - Asymptomatic vs very symptomatic
- Extent of radiograph abnormalities and whether there is evidence of progression?

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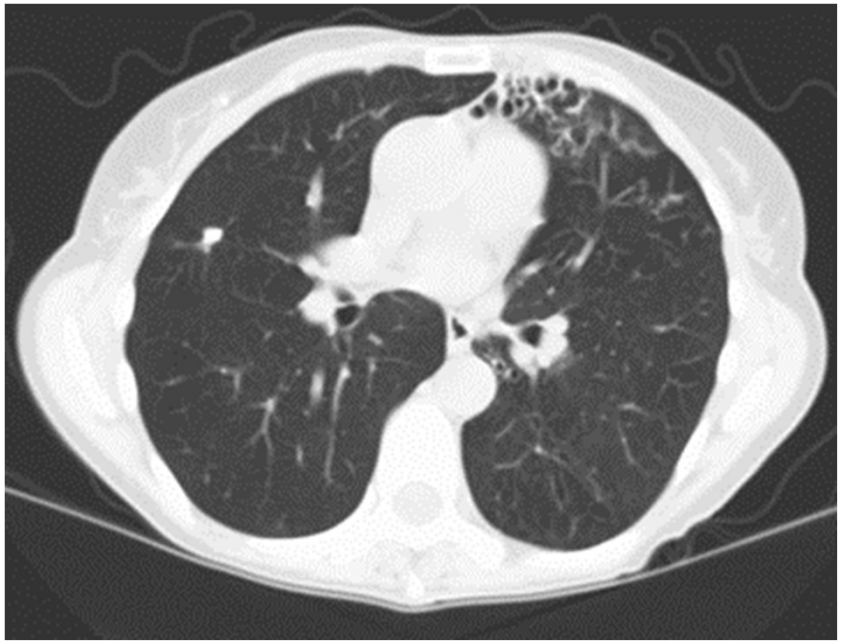
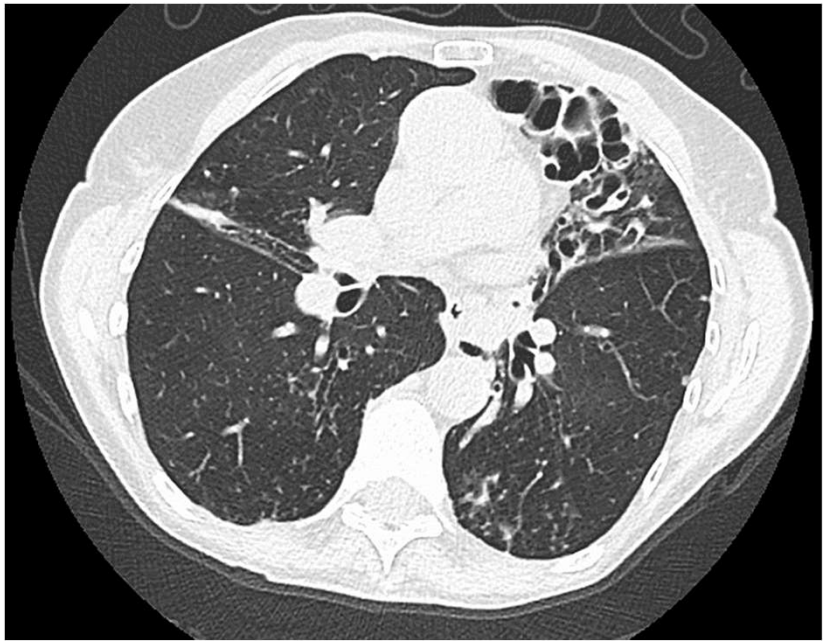
NTM Pulmonary Disease: Whom to Treat



65 yr old woman
Chronic cough

8 yrs



Diagnosed with MAC

”Bronchitis” 2-3 times/yr

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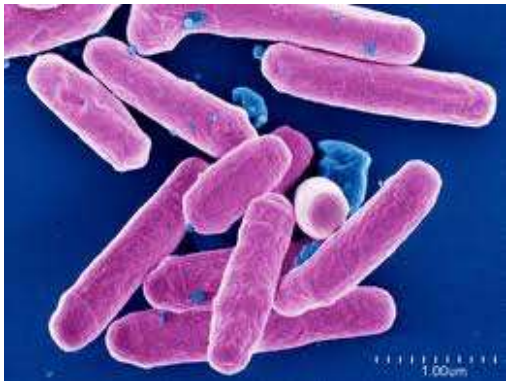
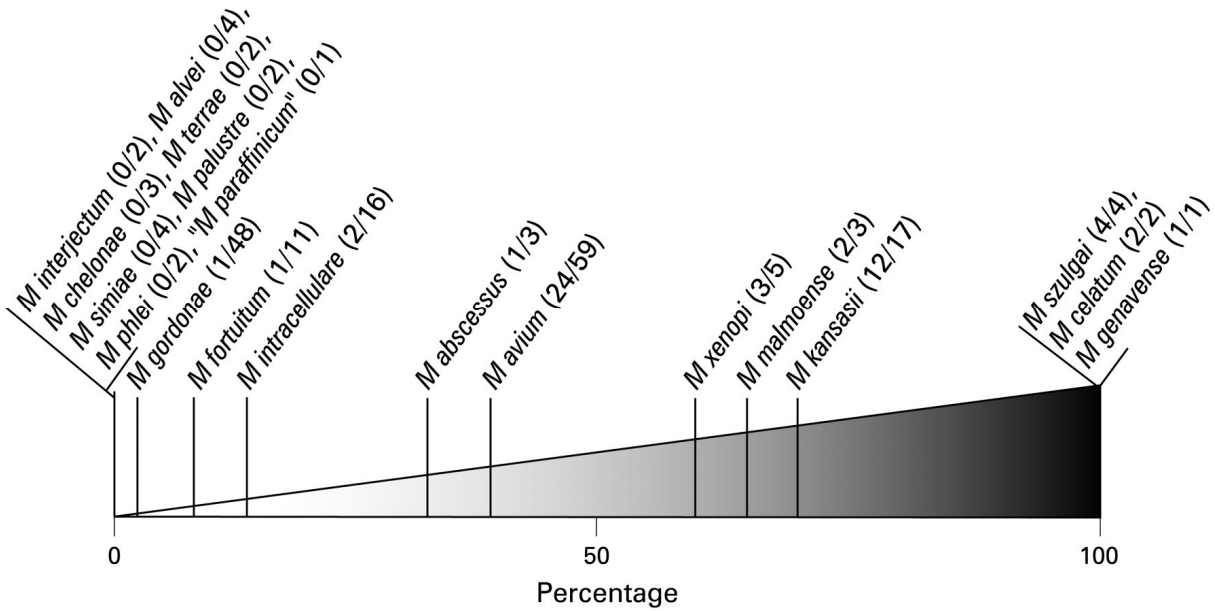
NTM Pulmonary Disease: Whom to Treat

The degree of pathogenicity (ability to cause disease) varies greatly among NTM

Organism





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NTM Pulmonary Disease: Whom to Treat

Goals of Treatment

What are we trying to achieve?

- Cure?
- Bacteriologic conversion?
- Relief of symptoms?
- Prevention of progression?
- All of the above!

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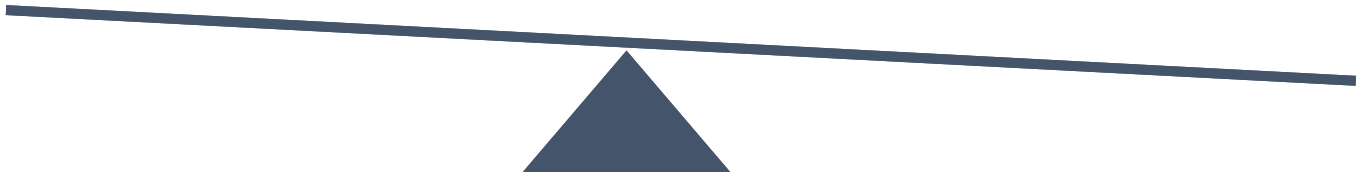
NTM: Treatment Outcomes by Species

NTM	Expected Cure
M. kansasii	≥ 95%
MAC	56% to 85% Depends on extent of disease
M. abscessus	25-80% Depends on subspecies

Decision to Treat

	Watchful Waiting	Initiate Treatment
NTM Species	Less virulent NTM	More virulent NTM
Disease Severity	No risk factors for progression: Noncavitary, AFB smear negative	Multiple risk factors for progression: Cavitary, AFB smear positive
Patient Priorities	Few symptoms, good quality of life	Many symptoms, poor quality of life



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Daley CL, et al. *CID* 2020;71:5-913 and *Euro Respir J* 2020;56:2000535

Why Early Diagnosis and Treatment Are Important

- Disease progression occurs within 3-5 years in ~60% of persons who meet ATS/IDSA diagnostic criteria[1-3]
- Lung function declines[4,5]
- 5-year all-cause mortality can be as high as 10%-33%[6-8]
  - Mortality is not usually due to NTM itself
  - Mortality higher in untreated than treated MAC (33% vs. 22%)[6]

1. Hwang JA, et al. *Eur Respir J*, 2017;49:1600537; 2. Kwon BS, et al. *Respir Med* 2019;150:45-50; 3. Moon SM, et al. *Respir Med* 2019;151:1-7; 4. Park HY, et al. *Chest* 2016;150:1222-1232; 5. Kimuzuka Y, et al. *PLoS ONE* 2019;14:e0216034; 6. Ito Y, et al. *Int J Tuberc Lung Dis* 2012;16:408-14; 7. Diel R, et al. *BMC Infect Dis* 2018;18:206; 8. Jhun BW, et al. *Eur Respir J* 2020;55:1900798.

Treatment of NTM: Background

- Treatment requires multidrug regimens
  - Varies by species
  - Frequently associated with side-effects
- Treatment duration is long
  - 12 mos after culture becomes negative (conversion)
- Treatment outcomes are suboptimal
  - Vary by species
  - High rates of recurrence and reinfection.

Griffith DE, et al. *Curr Opin Infect Dis*. 2012;25(2):218-227.

Mycobacterium avium Complex

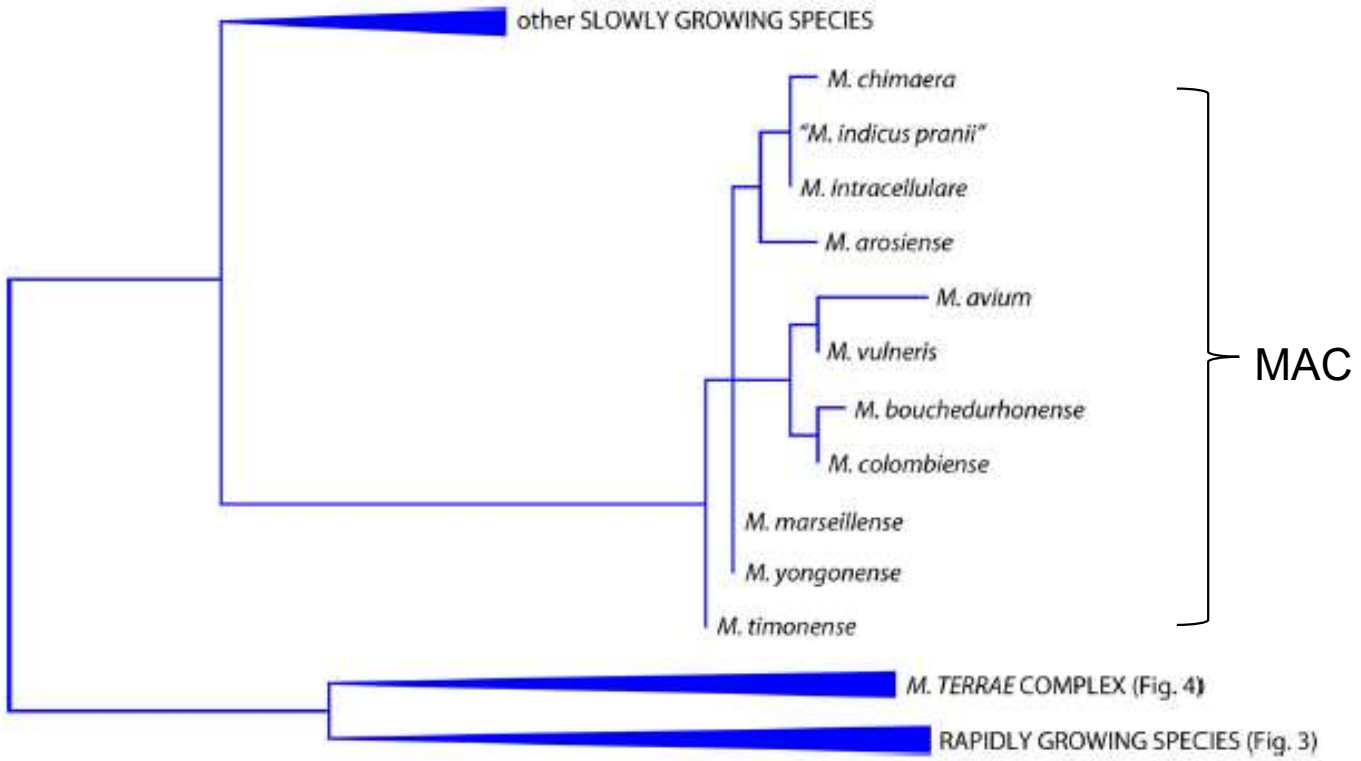

FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

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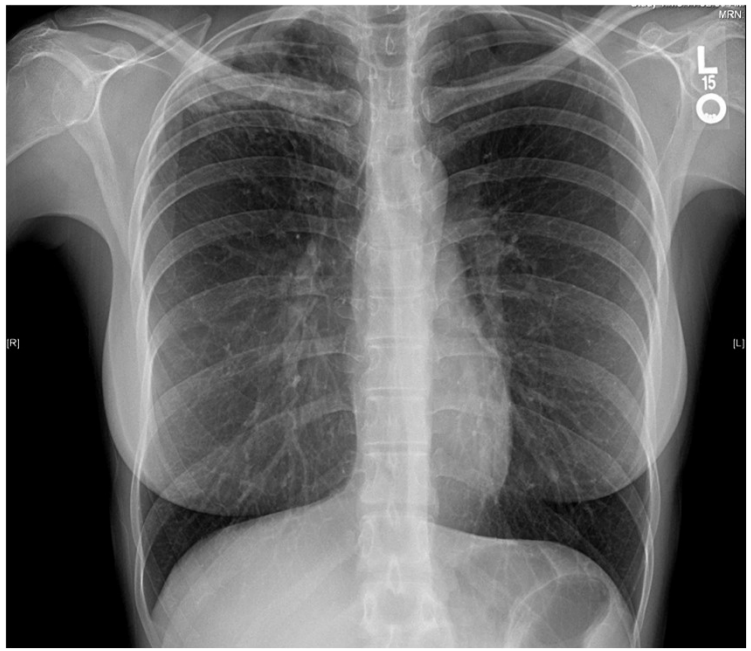
Tortoli E. Clin Micro Rev 2014;27:727-752

35 year old Caucasian woman with cough for several weeks



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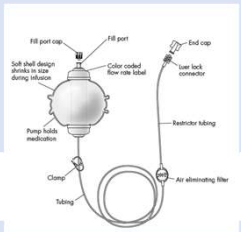
Drugs Used for the Treatment of MAC

First-Line Oral	Alternative Oral	Parenteral (IV, IM)	Inhaled
Macrolides azithromycin clarithromycin	**Fluoroquinolones** moxifloxacin ciprofloxacin	**Aminoglycosides** amikacin streptomycin	**Aminoglycosides** amikacin
Rifamycins rifampin riifabutin	**Oxazolidinones** linezolid tedizolid		
Ethambutol	Bedaquiline		
	Clofazimine		

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Mycobacteriology Laboratory Results

Common Report

Identification:
M. avium complex

Drug susceptibility:
Amikacin R
Clarithromycin S
Rifampin S
Ethambutol R
Linezolid R
Moxifloxacin I

Preferred Report

Identification:
100 colonies of *M. intracellulare ssp chimaera*

Drug susceptibility:	**MIC**
Amikacin	8
Clarithromycin	2
Linezolid	32
Moxifloxacin	2
Clofazimine	0.25

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Recommended Initial Treatment Regimens for MAC Pulmonary Disease

Phenotype	No. of Drugs	Preferred Regimen[a]	Dosing Frequency	Duration
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampin (rifabutin) Ethambutol	3 times weekly	12 months beyond culture conversion
Cavitary	≥ 3	Azithromycin (clarithromycin) Rifampin (rifabutin) Ethambutol Amikacin IV (streptomycin)[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

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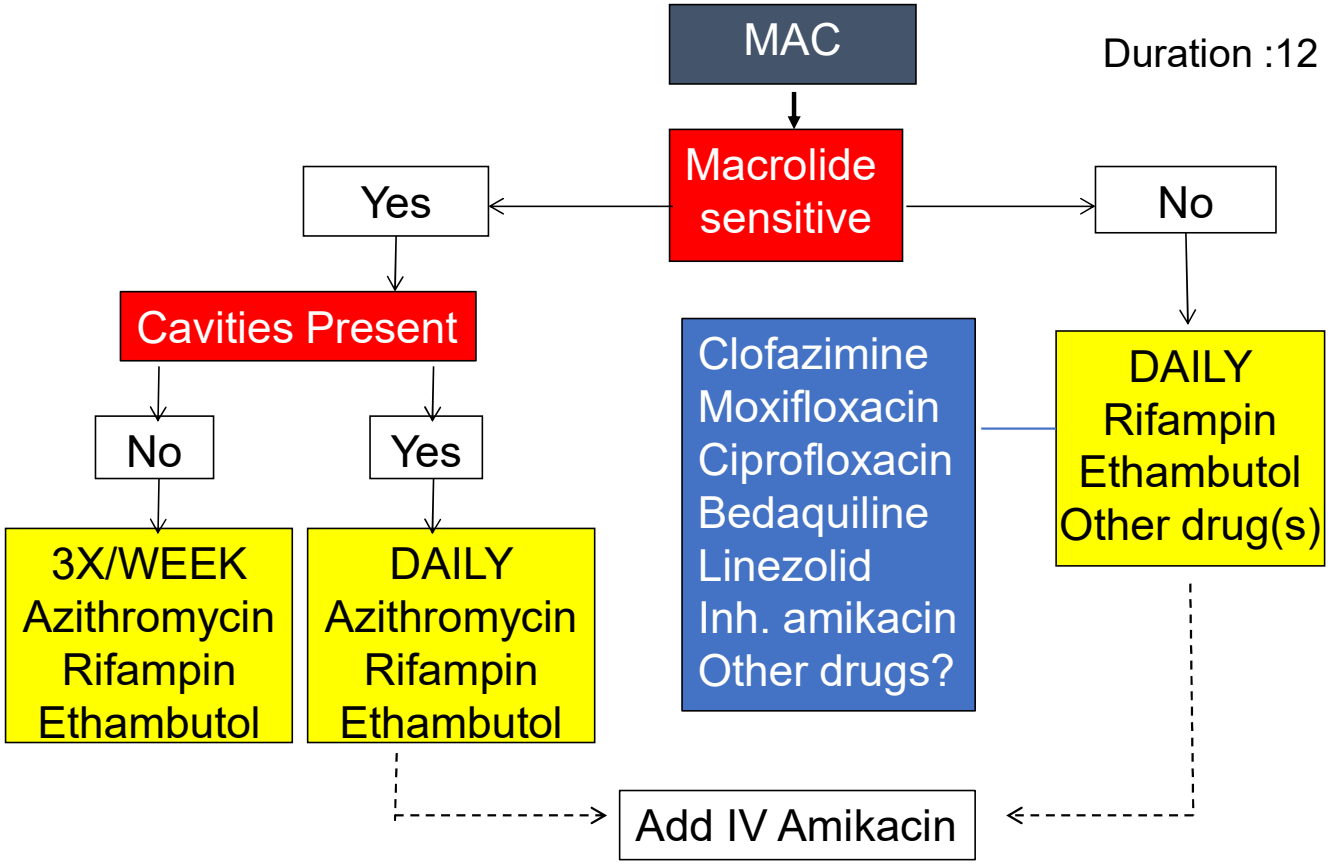
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

Treatment of Pulmonary *M. avium* complex



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Treatment Outcomes for MAC

	Culture Conversion	Microbiologic Recurrence	Reinfection
Macrolide susceptible			
Non cavitary Cavitary	70% - 80% 50% - 80%	25-48%	46-75%

Griffith DE et al. *Am J Respir Crit Care Med.* 2006;174:928-934.
Jeong BH et al. *Am J Respir Crit Care Med.* 2015;191:96-103.
Moon SM et al. *Eur Respir J.* 2016;50:1602503.
Wallace R et al. *Chest.* 2014;146:276-282.
Koh WJ et al. *Eur Respir J.* 2017;50.
Morimoto K et al. *Ann Am Thorac Soc.* 2016;11:1904.
Boyle DP et al. *Ann Am Thorac Soc.* 2016;13:1956-1961

Treatment Outcomes for MAC

	Culture Conversion	Microbiologic Recurrence	Reinfection
Macrolide susceptible			
Non cavitary Cavitary	70% - 80% 50% - 80%	25-48%	46-75%
Macrolide resistant			
No surgery/aminoglycoside* Some surgery/aminoglycoside Surgery + prolonged aminoglycoside*	5% 15% 80%	–	–

* ≥ 6 months parenteral aminoglycoside

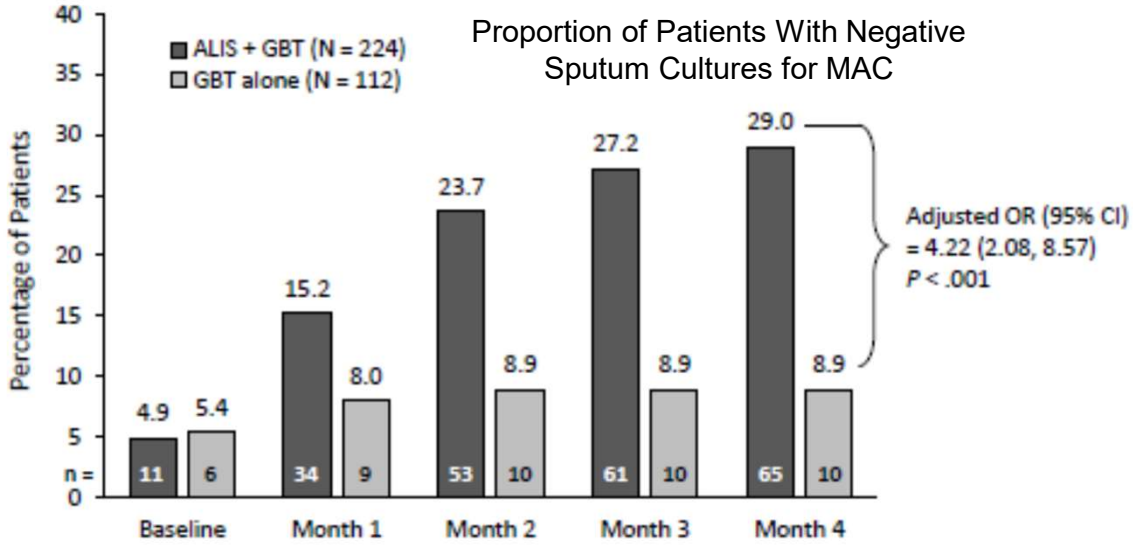
Griffith DE et al. *Am J Respir Crit Care Med.* 2006;174:928-934.
Jeong BH et al. *Am J Respir Crit Care Med.* 2015;191:96-103.
Moon SM et al. *Eur Respir J.* 2016;50:1602503.
Wallace R et al. *Chest.* 2014;146:276-282.
Koh WJ et al. *Eur Respir J.* 2017;50.
Morimoto K et al. *Ann Am Thorac Soc.* 2016;11:1904.
Boyle DP et al. *Ann Am Thorac Soc.* 2016;13:1956-1961

Treatment Refractory MAC Pulmonary Disease

Guideline recommendation

In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we recommend 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).

CONVERT Study – Randomized, controlled study of ALIS in treatment refractory MAC pulmonary disease



Griffith D, et al. AJRCCM 2018;198:1559-1569

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Recommended Treatment Regimens for MAC Pulmonary Disease

	No. of Drugs	Preferred Regimen[a]	Dosing Frequency
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥ 3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (IV aminoglycoside may be used 3 times weekly)
Refractory[c]	≥ 4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or IV (streptomycin)[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
c. Sputum culture positive after 6 months of guideline-based therapy

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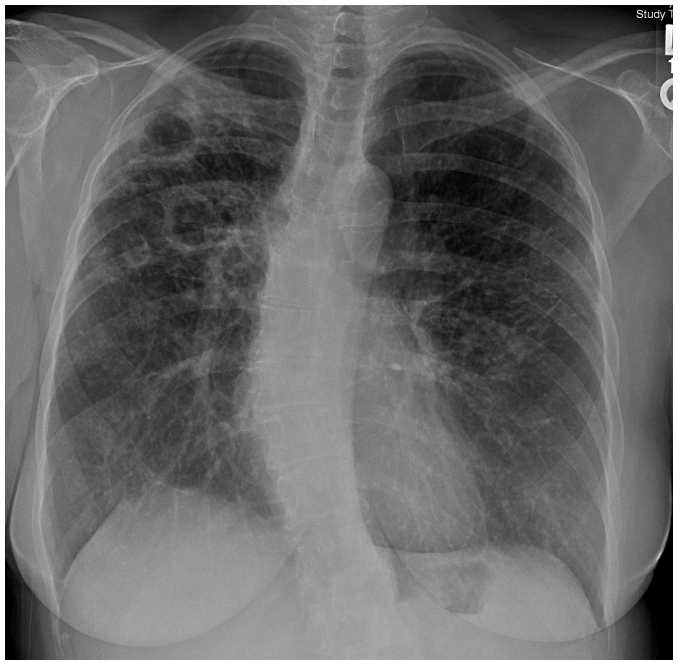
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

M. avium complexa: Summary

- MAC pulmonary disease should be treated with a macrolide-based regimen
- An aminoglycoside should be considered in cavitary disease and when macrolide resistance is present
- The optimal duration of therapy is not know but should be *at least* 12 months beyond the point of culture conversion
- Macrolide susceptible MAC is usually cured
- In treatment refractory MAC, amikacin liposome inhalation suspension should be added to guideline-based therapy
- Recurrences are common and usually due to reinfection with another strain (or species)

68 year old woman with chronic cough and fatigue



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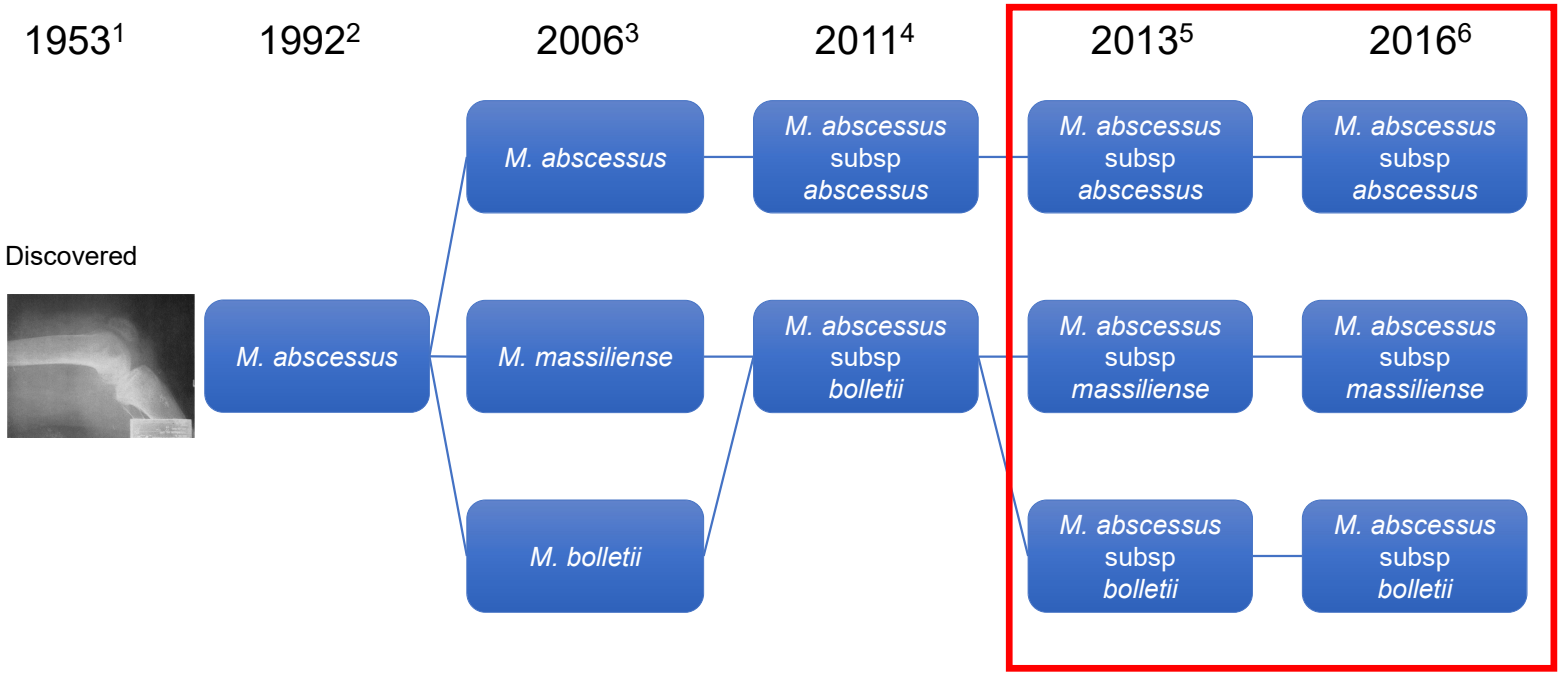
Mycobacterium abscessus: An Evolving Taxonomy



[1]Moore M J Invest Derm 1953;20:133
[2]Kusunoki S. Int J Syst Bacteriol 1992;42:240
[3]Adekambi T. Int J Syst Bacteriol 2006;56:133
[3]Adekambi T. Int J Syst Bacteriol 2006;56:2025
[4]Leao SC. Int J Syst Evol Microbiol 2011;61:2311
[5]Cho YJ. PLoS ONE 2013 8(11):e81560
[6]Tortoli E. Int J Syst Evol Microbiol 2016;66:4471

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Drugs Used for the Treatment of *M. abscessus*

First-Line Oral	Alternative Oral	Parenteral (IV, IM)	Inhaled
Macrolides azithromycin clarithromycin	**Fluoroquinolones** moxifloxacin ciprofloxacin	**Aminoglycosides** amikacin streptomycin	**Aminoglycosides** amikacin (off-label use)
Oxazolidinones linezolid tedizolid		**Carbapenems** imipenem meropenem	
Cycline omadacycline		**Cephalosporins** cefoxitin	
clofazimine bedaquiline		**Cyclines** tigecycline omadacycline eravacycline	

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Mycobacterium abscessus: Macrolide Resistance

***M. abscessus* is resistant to most antimicrobials**

Resistance to macrolides impacts treatment outcomes

Two types of resistance:

Mutational Resistance

Mutation in *rrl* gene

Inducible Resistance

Erythromycin ribosomal methylase gene, *erm*(41)

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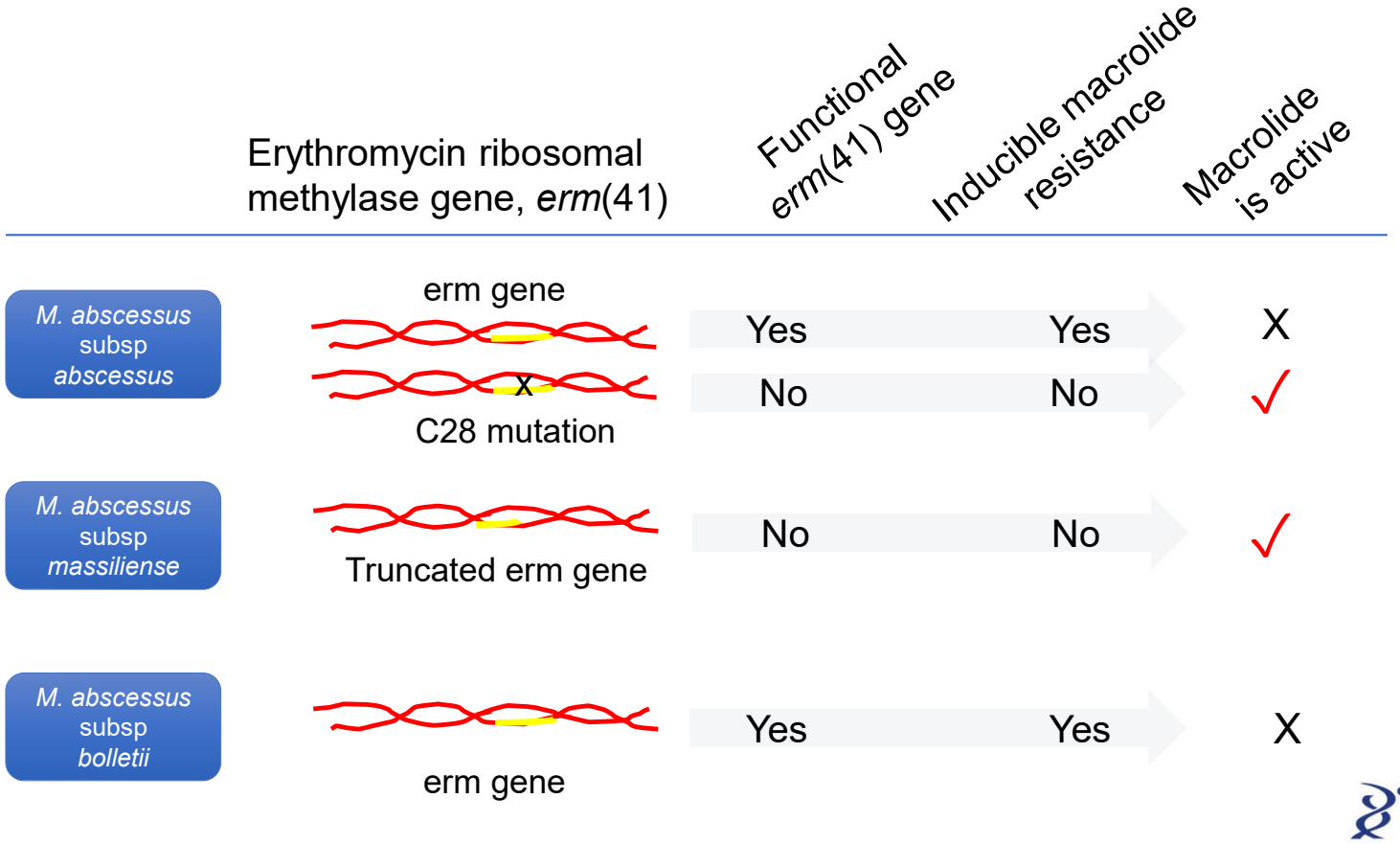
Mycobacterium abscessus: Inducible Macrolide Resistance



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Mycobacteriology Laboratory Results

Common Report

Identification:
M. chelonae-abscessus group

Drug susceptibility:
Amikacin R
Cefoxitin I
Clarithromycin S
Tigecycline S

Preferred Report

Identification:
200 colonies of *M. abscessus,* subspecies *abscessus*
erm(41) – present, T28C mutation

Drug susceptibility:	**MIC**
Amikacin	8
Cefoxitin	16
Clarithromycin	1
Imipenem	16
Tigecycline	0.125
Clofazimine	<0.5

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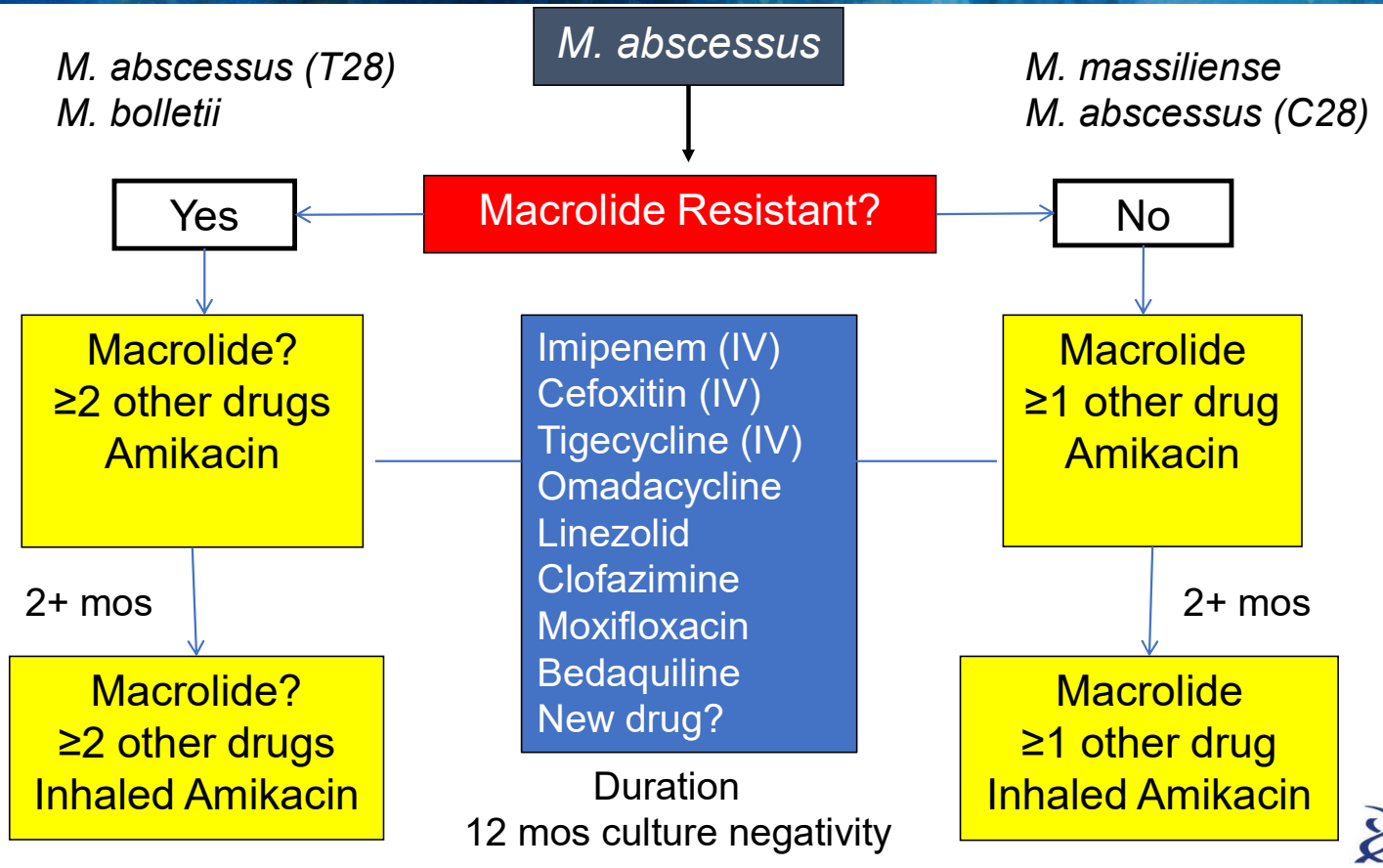
Treatment of *M. abscessus* complex



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Treatment Outcomes for *M. abscessus vs. M. massiliense*

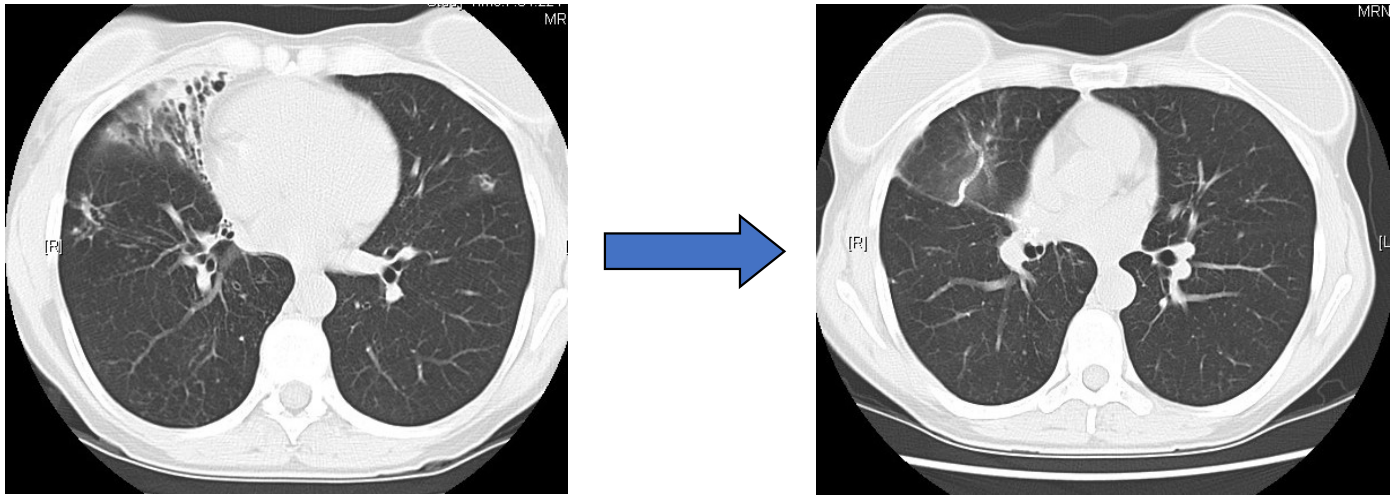
Study	Population	Treatment	N	Sputum conversion	Failure to convert	Recurrence*
Koh, 2011	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	24 33	25% **88%**	58% **3%**	17% **9%**
Lyu, 2014	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	26 22	42% **96%**	27% **0%**	31% **5%**
Roux, 2015	Cystic Fibrosis	*M. abscessus* *M. massiliense*	12 7	25% **86%**	- -	- -
Park, 2017	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	19 17	26% **82%**	74% **18%**	55% **0%**

*Most recurrences are due to reinfection

Koh WJ, et al. Am J Respir Crit Care Med 2011;183:405-10
Choi H, et al. Antimicrob Agents Chemother 2016 epub
Park J, et al. CID 2017;64:301-8

Surgery

56 year old Caucasian woman cleared her MAC but not the *M. abscessus*



Treatment Success

Jeon, 2009	58% (med) vs 88% (med+surg)
Jarand, 2011	39% (med) vs 65% (med+surg)

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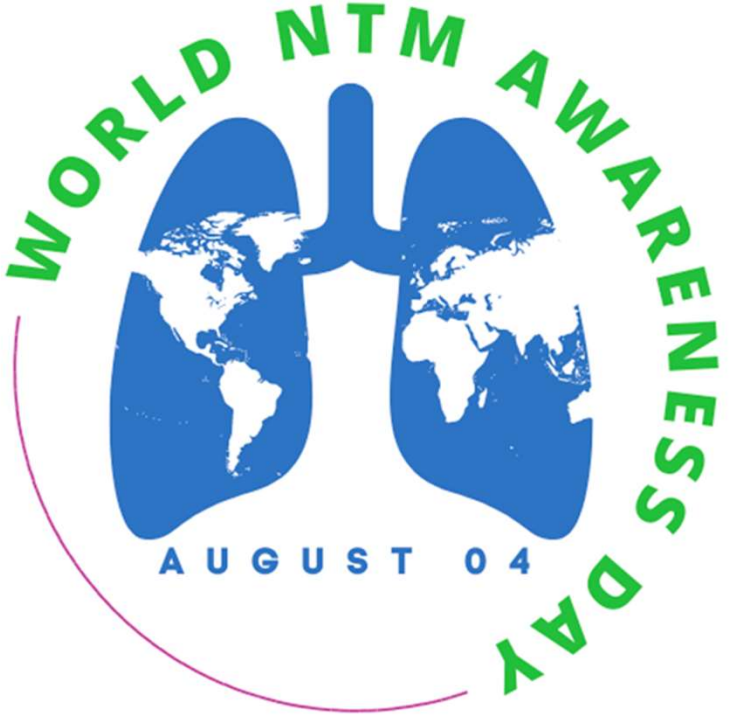
M. abscessus: Summary

- *M. abscessus* has high levels of *in vitro* resistance to many antibiotics
- Treatment requires a combination of intravenous, oral, and inhaled antibiotics
- Treatment outcomes are usually good when the *erm*(41) gene is not functional
- Most recurrences appear to be due to reinfection or another species
- Surgical resection may increase bacteriologic conversion

World NTM Awareness Day!



National Jewish Health