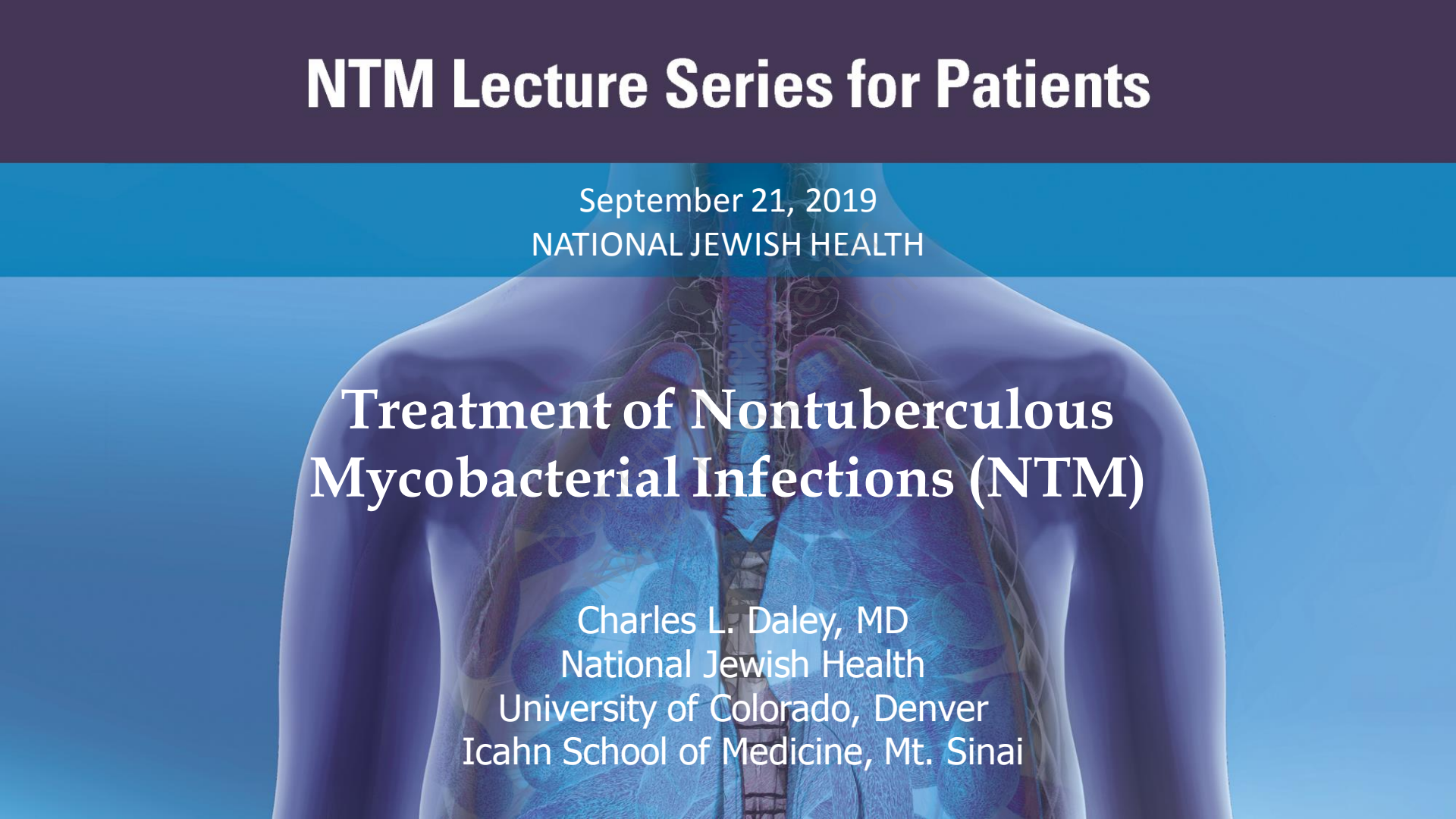
NTM Lecture Series for Patients

September 21, 2019
NATIONAL JEWISH HEALTH



Treatment of Nontuberculous Mycobacterial Infections (NTM)

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Disclosures

- Research Grant
  - Insmed
  - Spero
- Advisory Board:
  - Insmed
  - Johnson and Johnson
  - Spero Pharmaceuticals
  - Horizon Pharmaceuticals
  - Paratek
  - Meiji

NTM That Have Been Reported to Cause Lung Disease

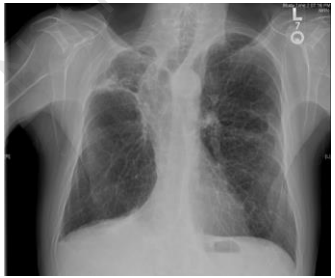
Slowly Growing Mycobacteria		Rapidly Growing Mycobacteria*	
M. arupense	*M. kubicae*	***M. abscessus***	*M. holsaticum*
M asiaticum	*M. lentiflavum*	*M. alvei*	*M. fortuitum*
M. avium	*M. malmoense*	*M. boenickei*	*M. mageritense*
M. branderi	*M. palustre*	***M. bolletii***	***M. massiliense***
M. celatum	*M. saskatchewanse*	*M. brumae*	*M. mucogenicum*
M. chimaera	*M. scrofulaceum*	*M. chelonae*	*M. peregrinum*
M. florentinum	*M. shimodei*	*M. confluentis*	*M. phocaicum*
M. heckeshornense	*M. simiae*	*M. elephantis*	*M. septicum*
M. intermedium	*M. szulgai*	*M. goodii*	*M. thermoresistible*
M. interjectum	*M. terrae*		
M. intracellulare	*M. triplex*		
M. kansasii	*M. xenopi*	* Growth in subculture within 7 days	

ATS Diagnostic Criteria For NTM Lung Disease

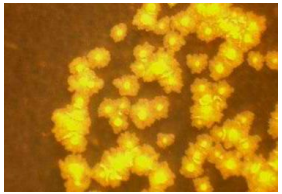
Clinical

Cough
Fatigue
Weight Loss

Radiographs



Bacteriology



≥ 2 positive
sputum cultures

ATS/IDSA AJRCCM 2007;175:367

NTM Pulmonary Disease

Whom to Treat

Patient

Organism

Goals of Treatment

NTM Pulmonary Disease

Whom to Treat

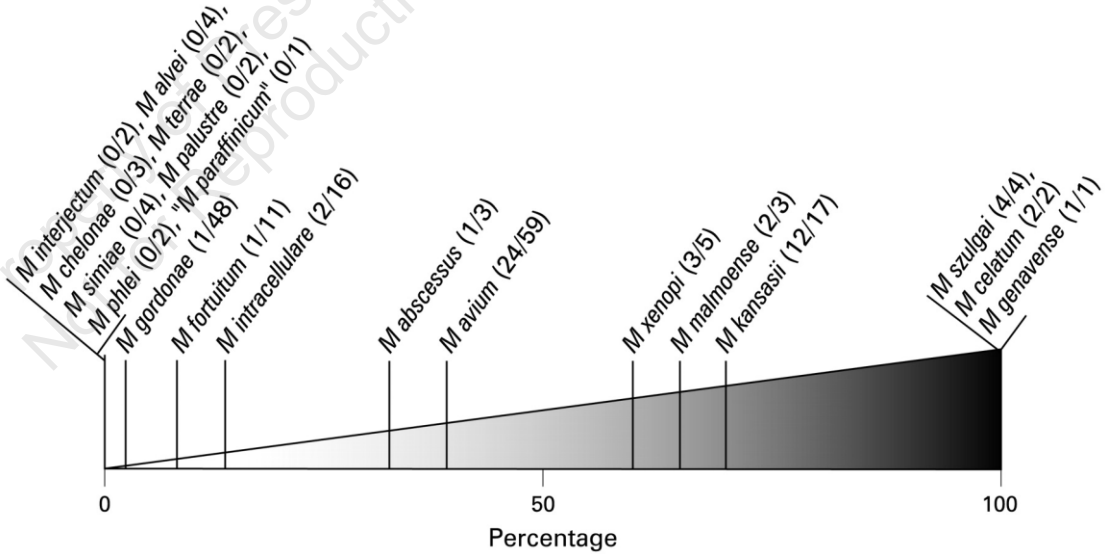
Patient

- Increased susceptibility?
- Clinical symptoms and overall condition of patient
- Extent of radiograph abnormalities and whether there is evidence of progression

NTM Pulmonary Disease

Whom to Treat

Organism



NTM Pulmonary Disease

Whom to Treat

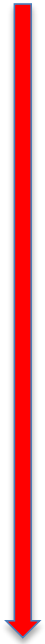
Goals of Treatment

- Cure?
- Bacteriologic conversion
- Relief of symptoms
- Prevention of progression

NTM

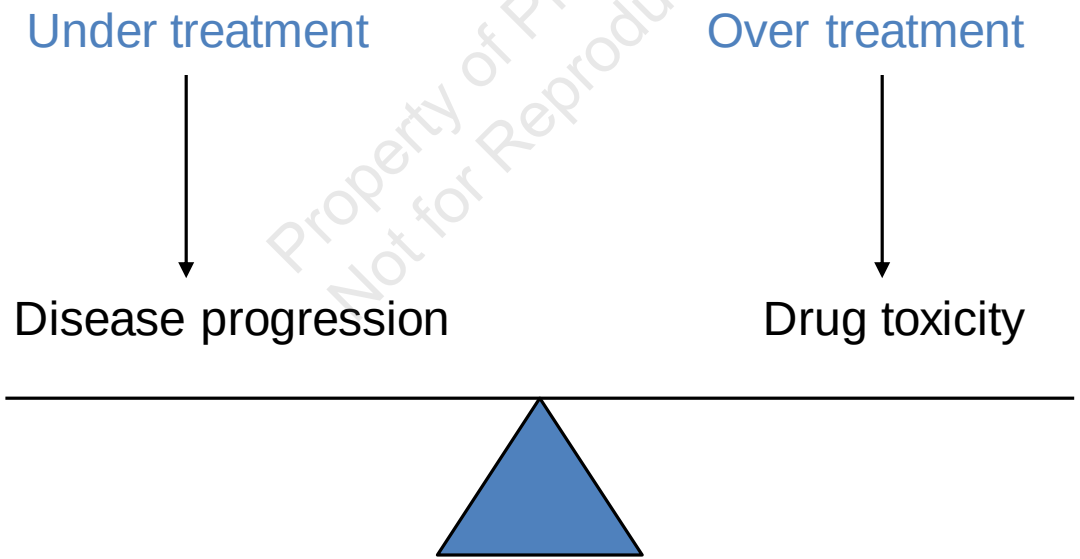
Treatment Outcomes

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



NTM Pulmonary Disease

Whom to Treat



Treatment of NTM

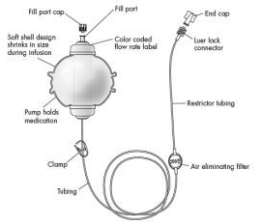
Background

- 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.

Drugs Used for the Treatment of NTM

Oral	Parenteral	Inhaled
Macrolides (azithromycin, clarithromycin)	**Aminoglycosides (streptomycin, amikacin)**	**Aminoglycosides** (amikacin)
Rifamycins (rifampin, rifabutin)	**Carbapenems (imipenem, meropenem)**	
Ethambutol	**Cefoxitin**	
Isoniazid	**Tigecycline**	
Fluoroquinolones (moxifloxacin, ciprofloxacin)		
Cyclines (doxycycline, minocycline)		
Sulfonamides		
Oxazolidinones (linezolid, tedizolid)		
Clofazimine		



- 35 year old Caucasian woman from Florida with cough for several weeks

Mycobacterium avium Complex

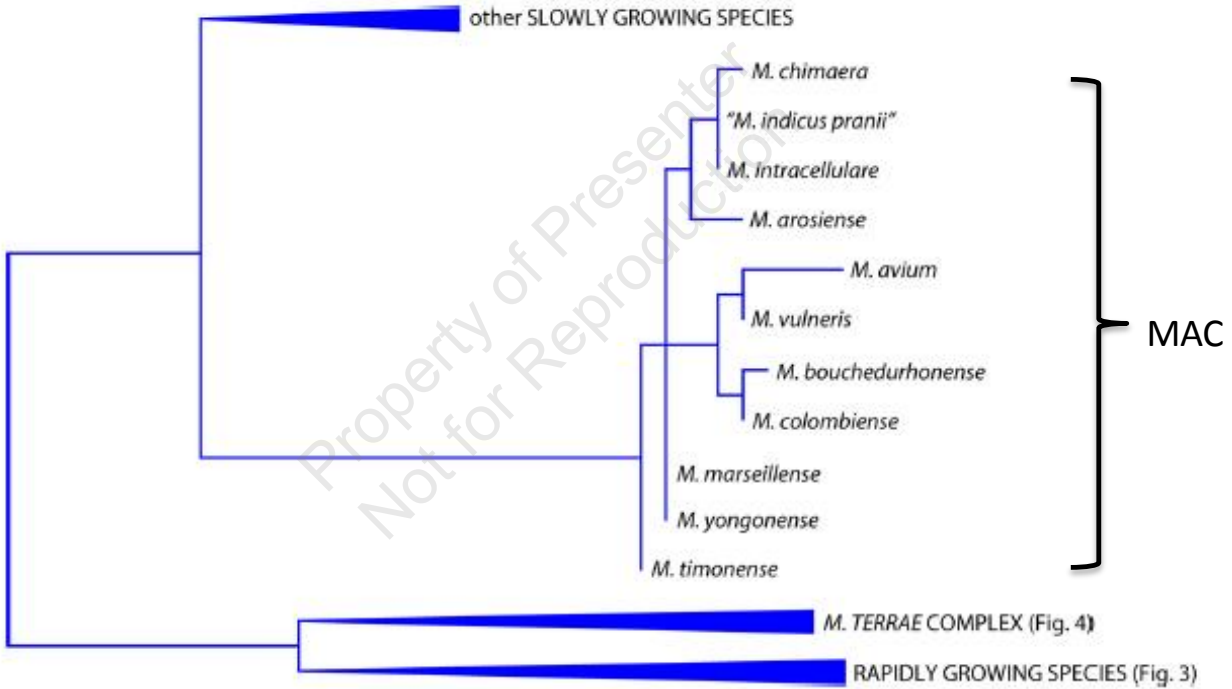


FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

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

Mycobacteriology Laboratory Results

Common Report

Identification:
M. avium complex

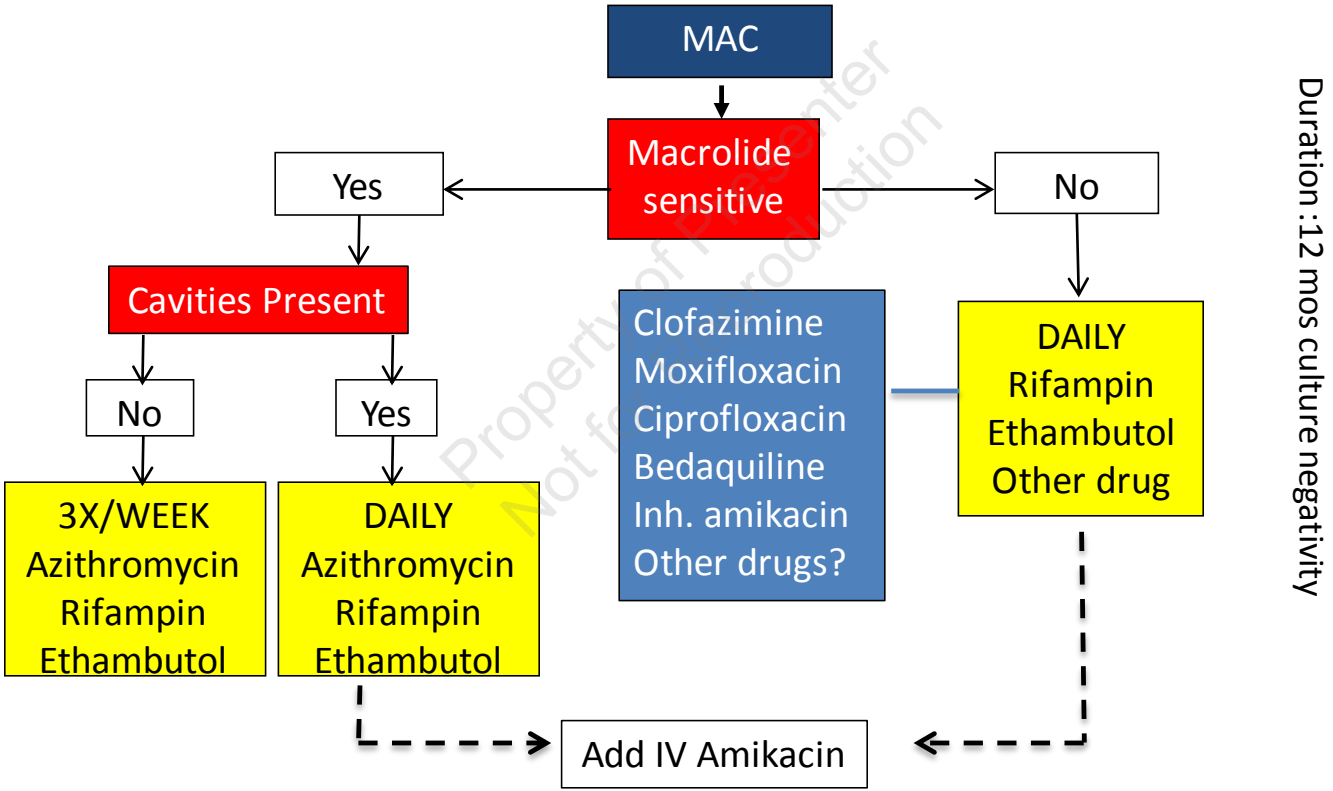
Drug susceptibility:
Amikacin R
Clarithromycin S
Rifampin S
Ethambutol R
Linezolid R
Moxifloxacin I

Preferred Report

Identification:
100 colonies of *M. chimaera*

Drug susceptibility:	**MIC**
Amikacin	8
Clarithromycin	2
Rifampin	0.5
Ethambutol	10
Linezolid	32
Moxifloxacin	2
Clofazimine	0.25

Treatment of Pulmonary *M. avium* complex



Treatment Outcomes for MAC

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

* ≥ 6 months IV aminoglycoside

Griffith DE, et al. AJRCCM 2006;174:928
Jeong BH, et al. AJRCCM 2015;191:96-103
Moon SM, et al. Antimicrob Agents Chemother; 2016
Wallace R, et al. Chest 2014;146:276-282
Koh WJ, et al. Eur Respir J 2017;50

MAC Recurrences After Completion of Therapy:
Relapse vs reinfection

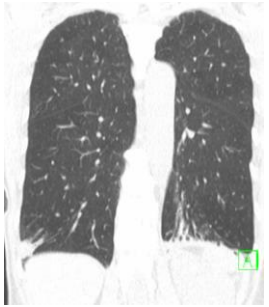
	University of Texas, Tyler [1]	Northwestern, Chicago, IL [2]	Samsung, Seoul, Korea[3]
Number of patients	155	190	402
Microbiologic recurrence	48%	25%	29%
New infection	75%*	46%*	74%**

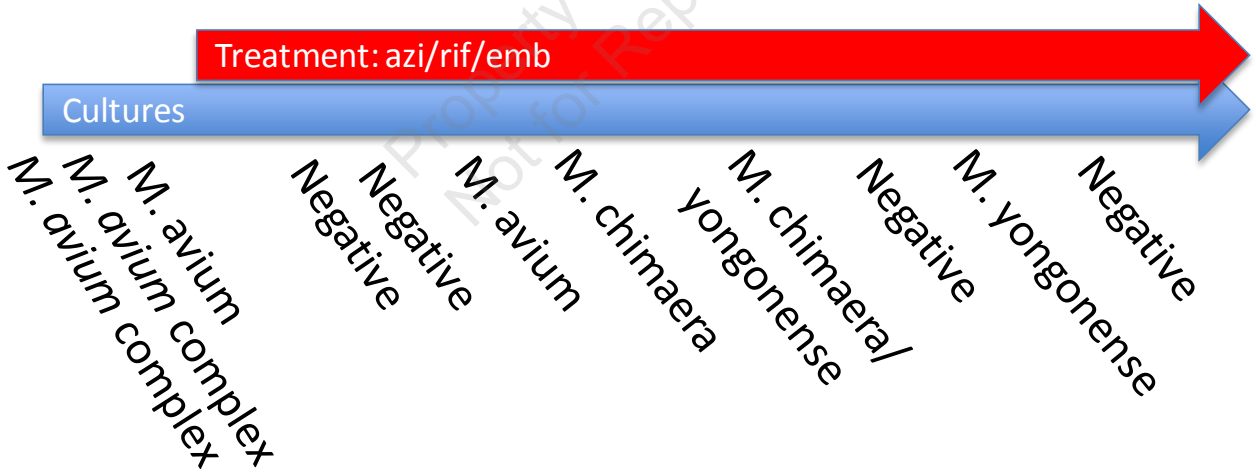
*Determined by pulse field electrophoresis
**Determined by rep-PCR

1. Wallace R, et al. Chest 2014;146:276-282
2. Boyle DP, et al. Ann Am Thorac Soc 2016
3. Koh WJ, et al. ERJ 2017;50 epub

Mixed Infection with Different MAC Species

62 y/o woman with
fatigue and chronic cough



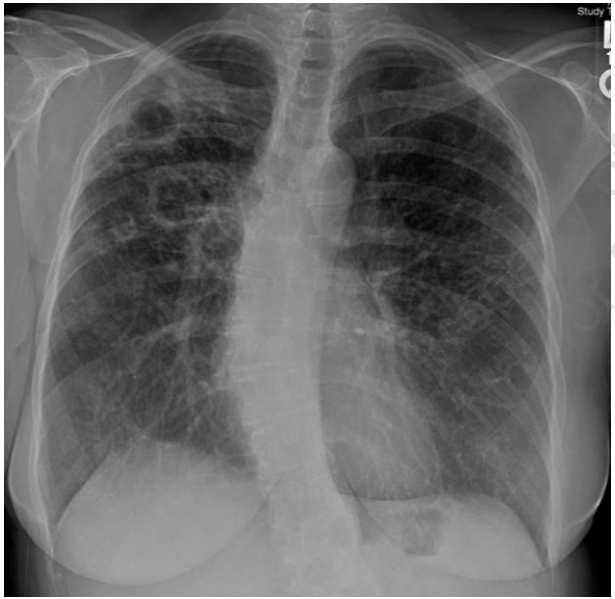


M. avium complex

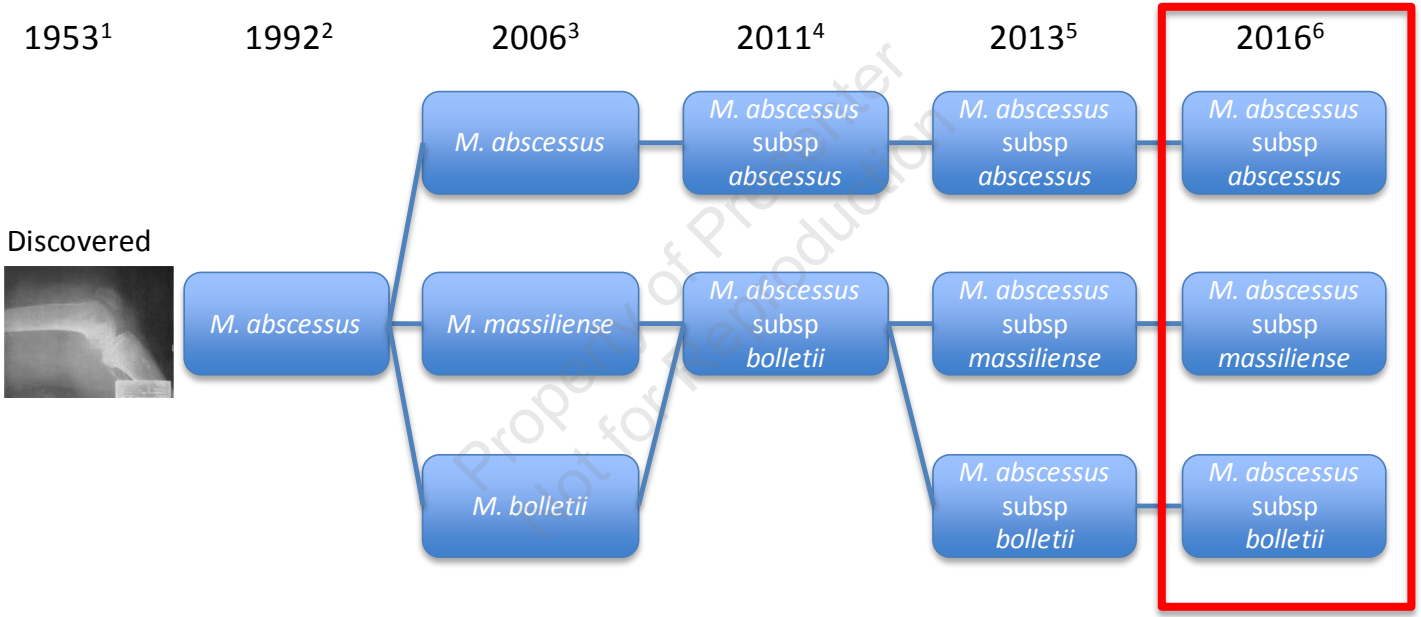
Summary

- 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
- Recurrences are common and usually due to reinfection with another strain (or species)

- 68 year old woman with chronic cough and fatigue



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
[7]Adekambi T. Int J Syst Evol Microbiol 2017;67:2726

Mycobacterium abscessus: Macrolide Resistance

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

Resistance to macrolides impacts treatment outcomes

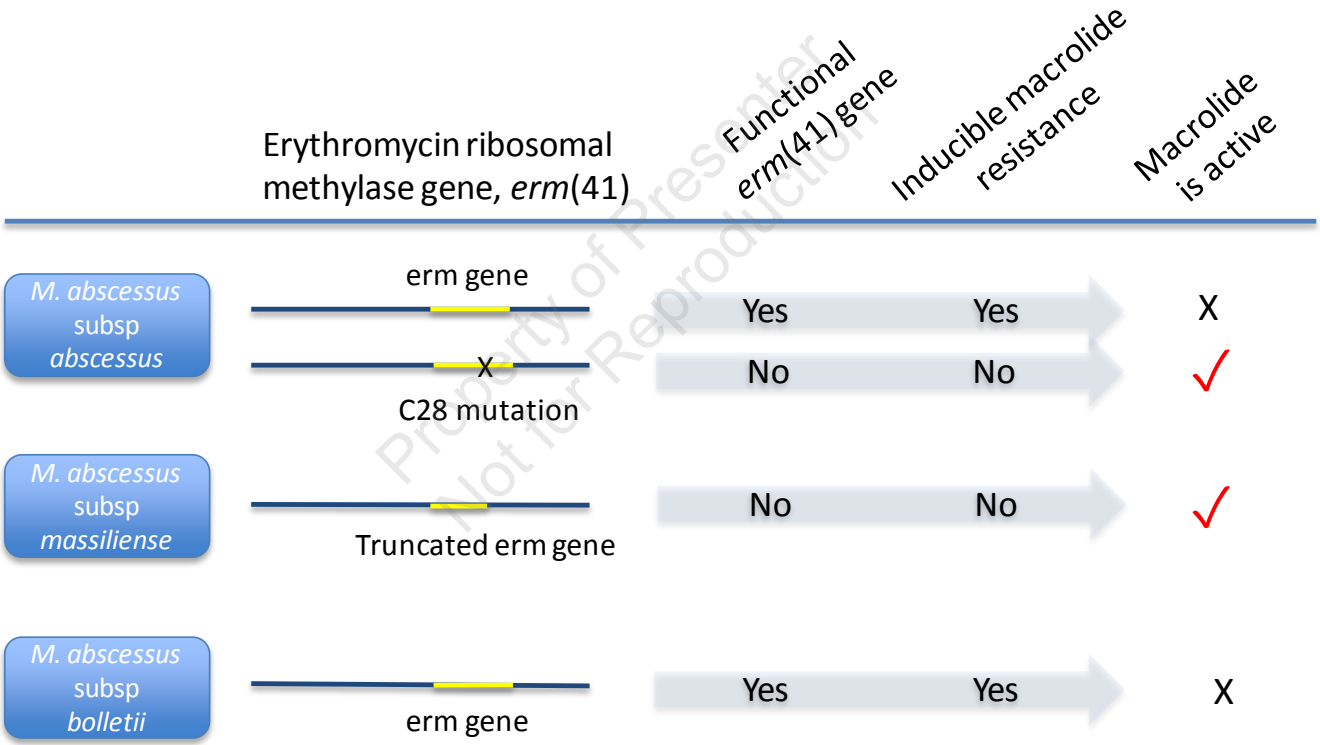
Mutational Resistance

Mutation in *rrl* gene

Inducible Resistance

Erythromycin ribosomal methylase gene, *erm*(41)

Mycobacterium abscessus: Inducible Macrolide Resistance



Mycobacteriology Laboratory Results

Common Report

Identification:
M. chelonae-abscessus group

Drug susceptibility:
Amikacin R
Cefoxitin I
Clarithromycin S
Tigecycline S

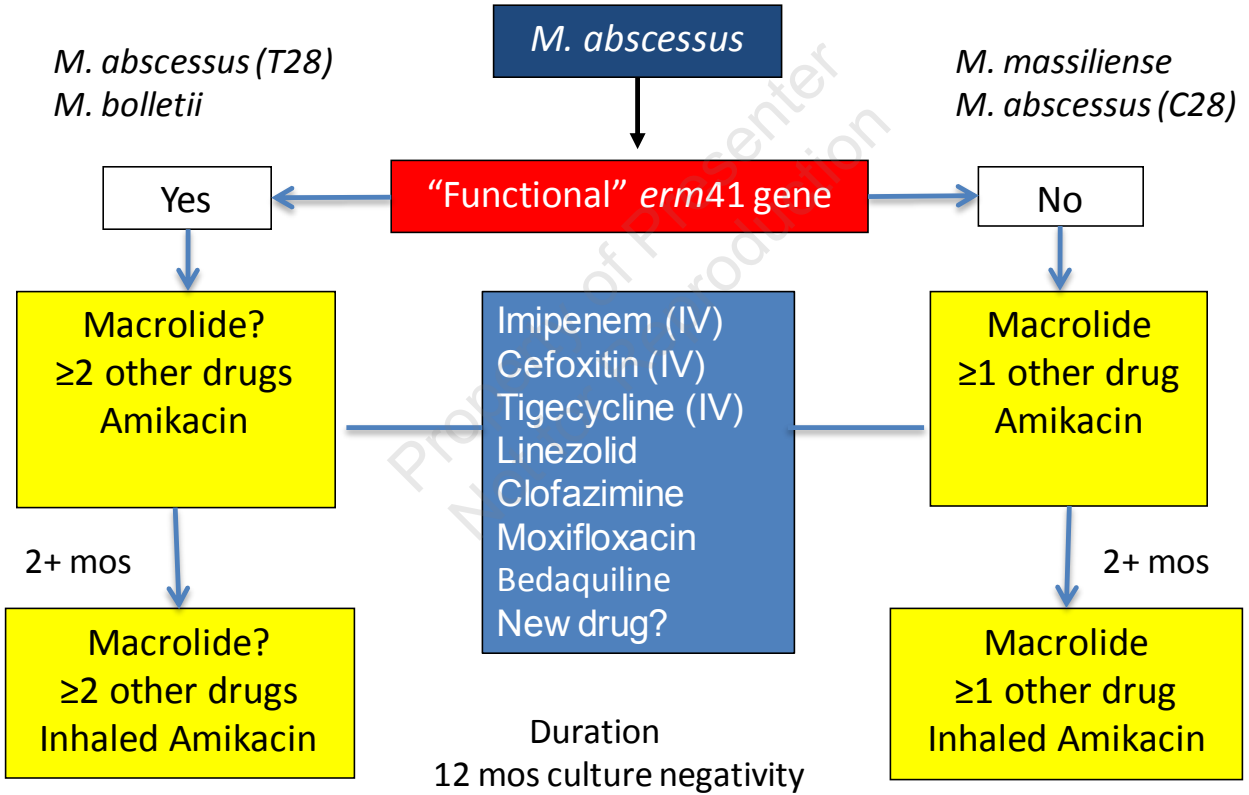
Preferred Report

Identification:
200 colonies of *M. abscessus,* subspecies *abscessus*

erm(41) – present, T28 mutation

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

Treatment of *M. abscessus* complex



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

Study	Population	Treatment	N	Sputum conversion	Failure to convert	Relapse
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%**

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

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 in not functional
- Most recurrences appear to be due to reinfection or another species
- Surgical resection may increase bacteriologic conversion