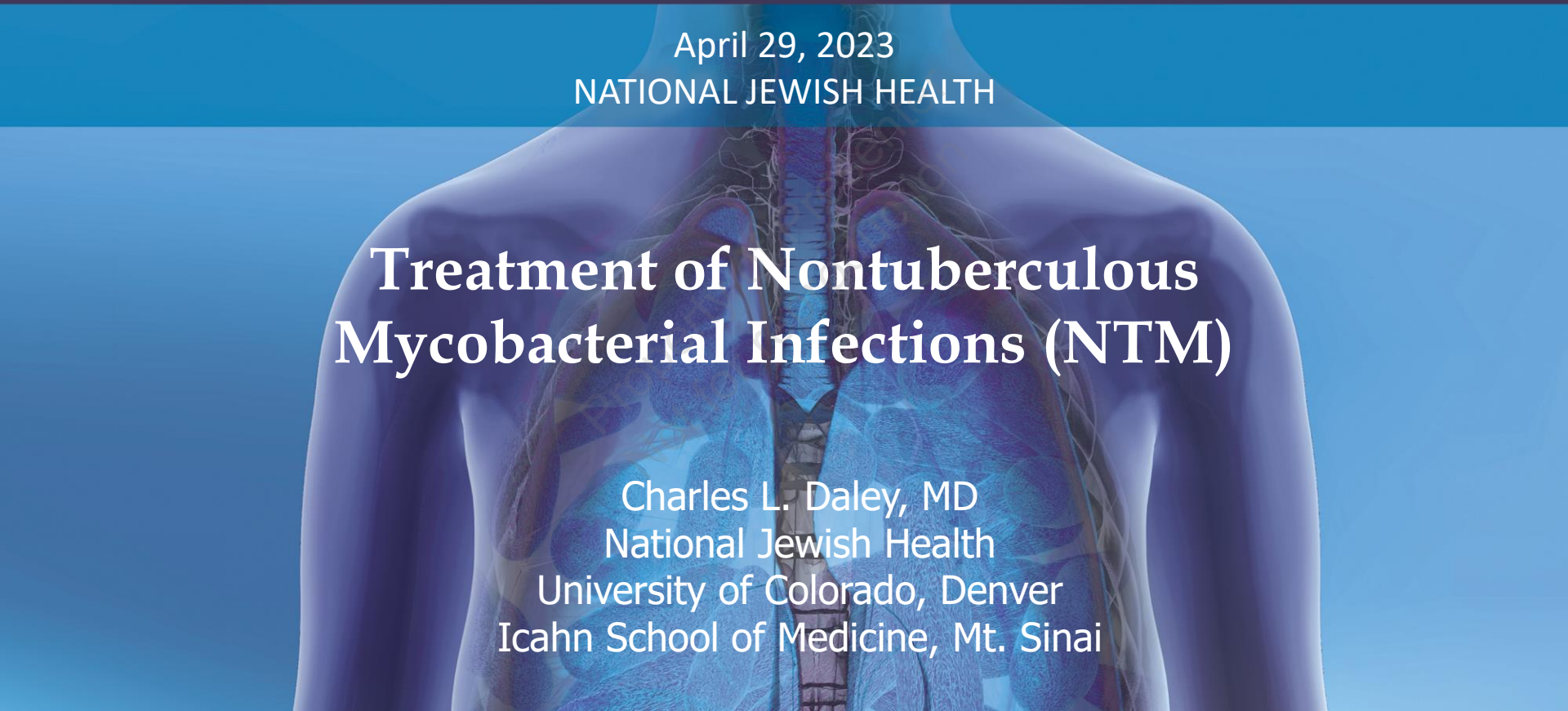
NTM Lecture Series for Patients

April 29, 2023
NATIONAL JEWISH HEALTH



Treatment of Nontuberculous Mycobacterial Infections (NTM)

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Icahn School of Medicine, Mt. Sinai

DISCLOSURES:

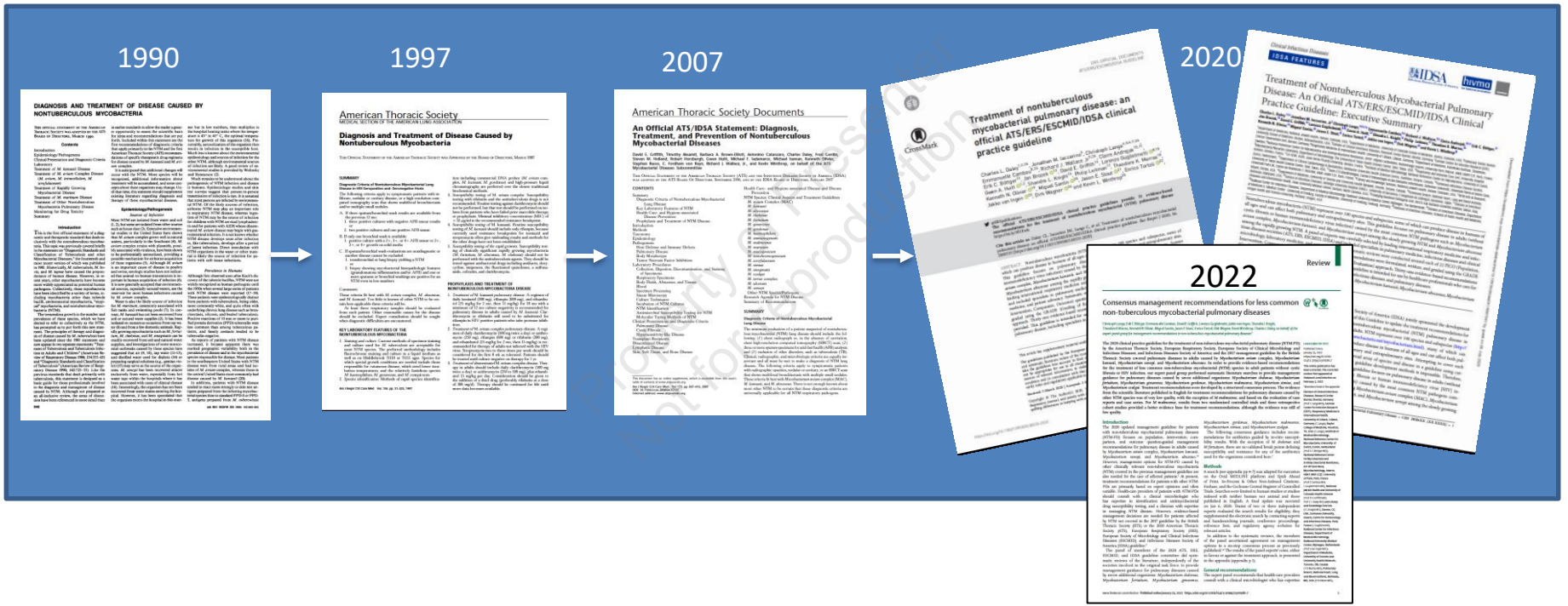
Consultant: Genentech, Pfizer

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

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

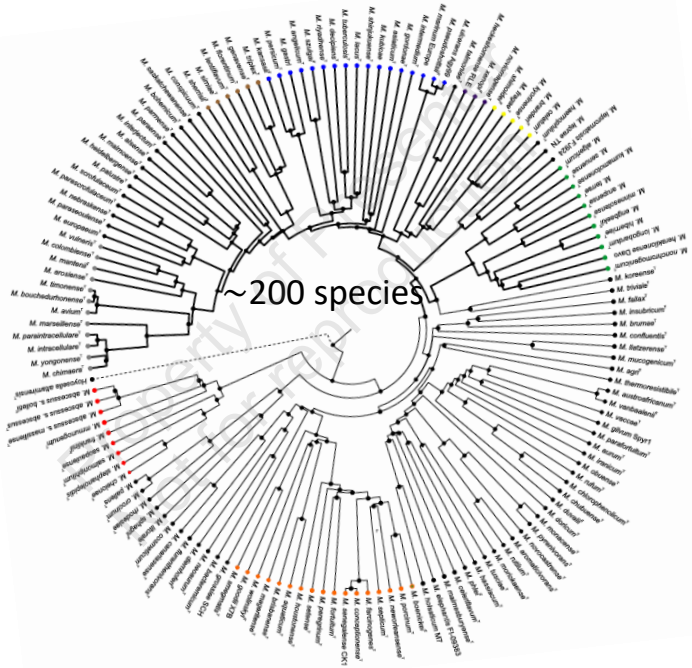
Contracted Research: AN2 Therapeutics, Bugworks, Insmed, Paratek Pharmaceuticals

NTM Lecture Series for Patients



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

NTM Treatment Guidelines



Slow Growers
***M. avium* complex**
M. kansasii
M. Xenopi

Rapid Growers
M. abscessus

Slow Growers
M. malmoense
M. simiae
M. szulgai
M. genevense
M. Gordonae

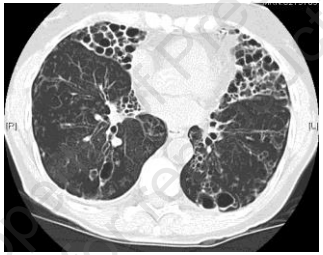
Rapid Growers
M. chelonae
M. fortuitum

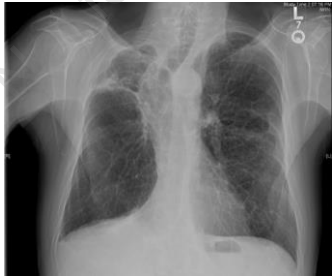
ATS Diagnostic Criteria For NTM Lung Disease

Clinical

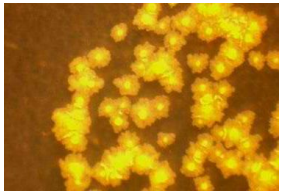
Cough
Fatigue
Weight Loss

Radiographs





Bacteriology



≥ 2 positive sputum cultures

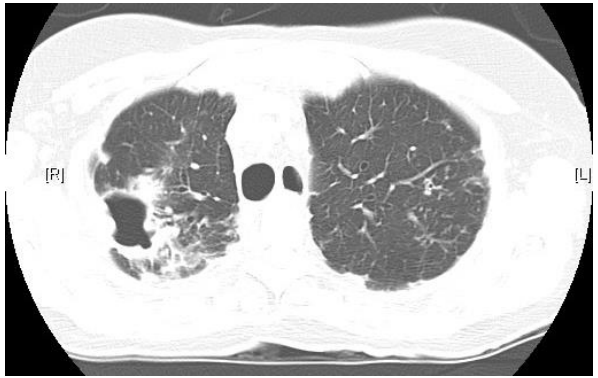
Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

NTM Pulmonary Disease

Whom to Treat

Consider the:

Patient



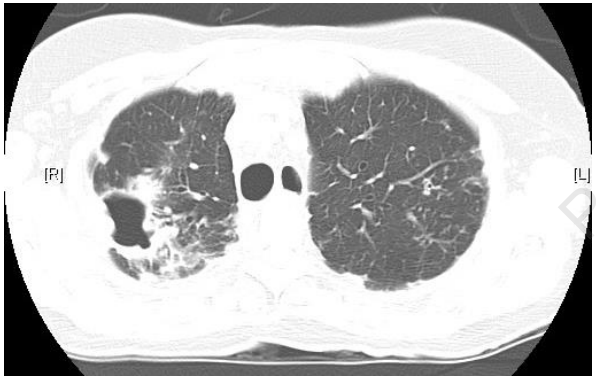
Organism

Goals of Treatment

NTM Pulmonary Disease

Whom to Treat

Patient

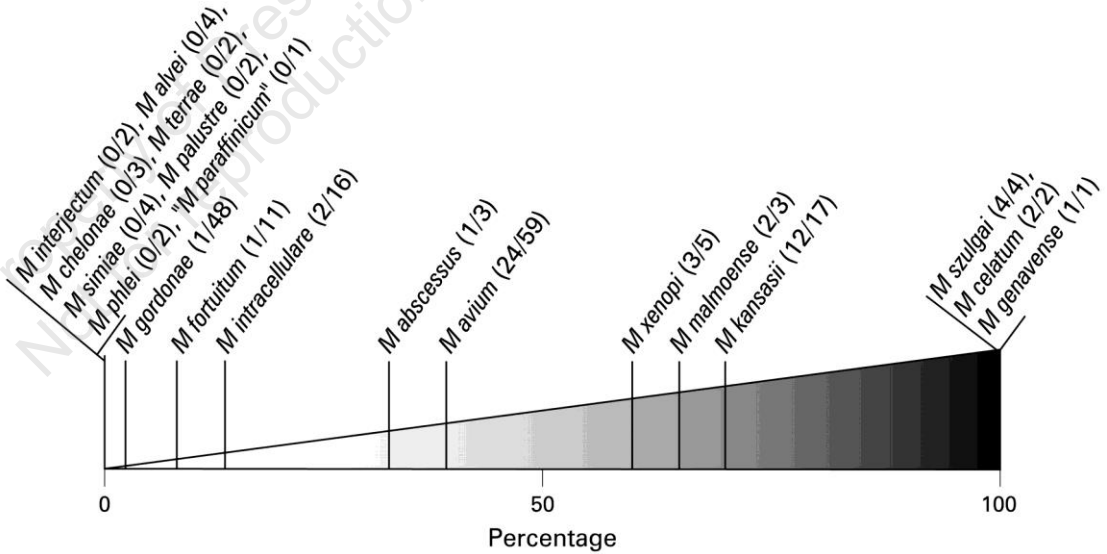


- Increased susceptibility?
- Clinical symptoms and overall condition of patient?
- Extent of radiograph abnormalities and whether there is evidence of progression?

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?

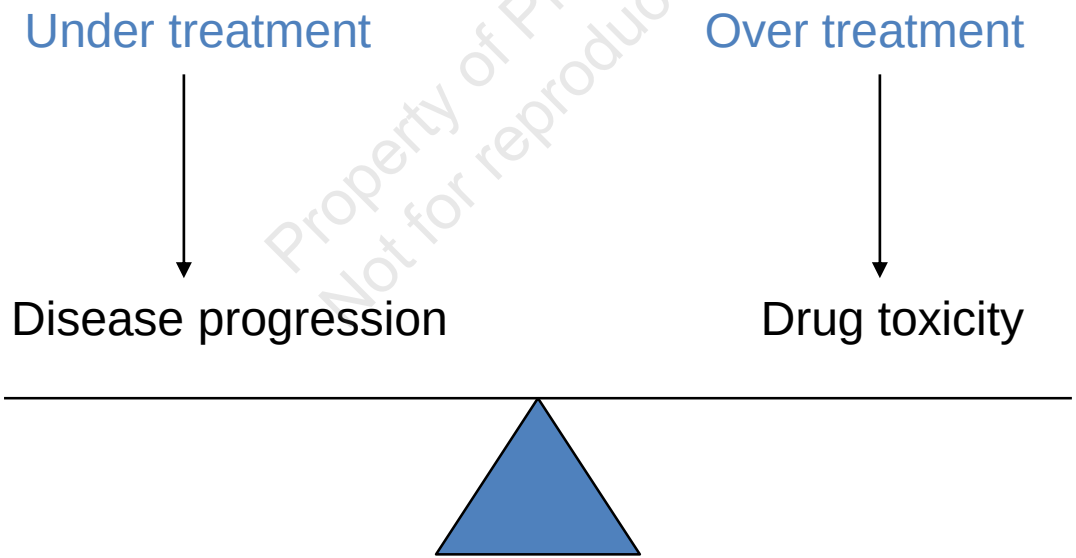
NTM

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

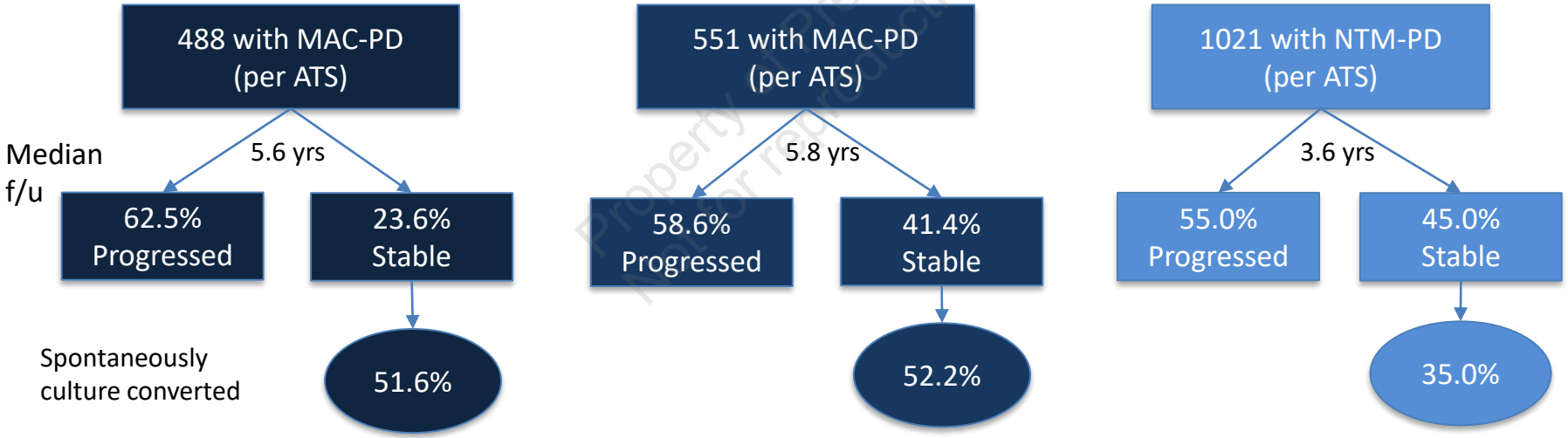
Whom to Treat



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

Moon SM, et al.
Resp Med 2019;151:1-7.

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

Treatment of NTM

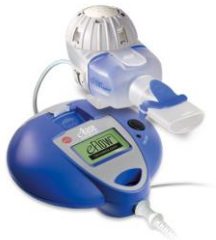
Background

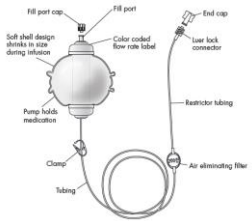
- Treatment requires multidrug regimens
  - Varies by species
  - Frequently associated with side-effects
- Treatment duration is long
  - 12 mos after culture becomes negative (conversion)
- Treatment outcomes are suboptimal
  - Vary by species
  - High rates of recurrence and reinfection.

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

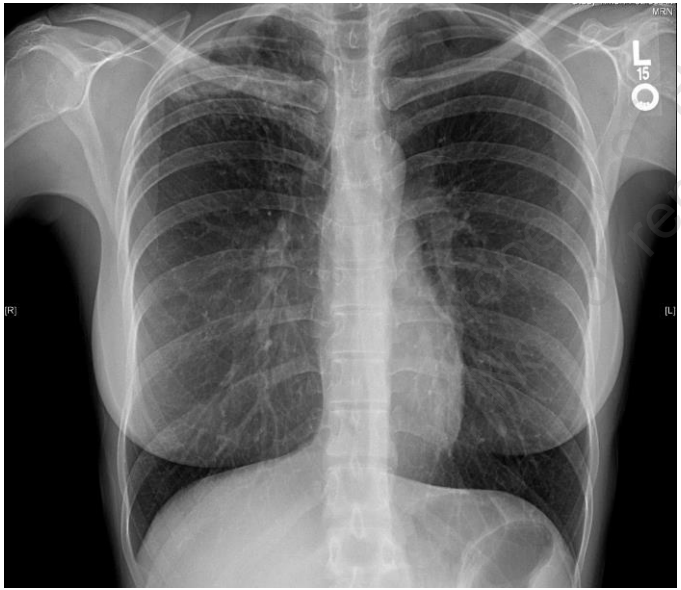
Drugs Used for the Treatment of NTM

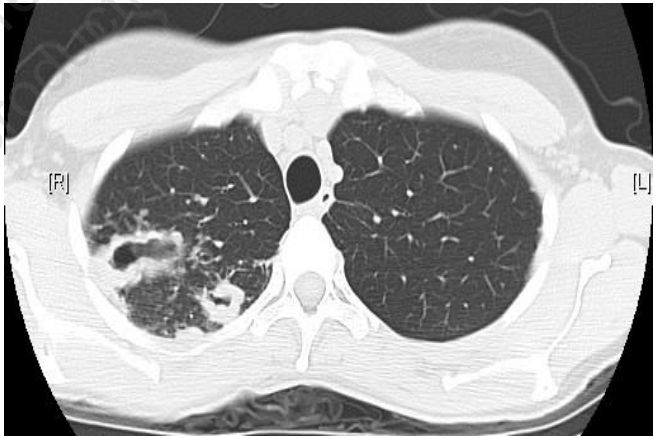
Oral	Parenteral	Inhaled
Macrolides (azithromycin, clarithromycin)	**Aminoglycosides (streptomycin, amikacin)**	**Aminoglycosides** (amikacin)
Rifamycins (rifampin, rifabutin)	**Carbapenems (imipenem, meropenem)**	
Ethambutol	**Cefoxitin**	
Isoniazid	**Tigecycline**	
Fluoroquinolones (moxifloxacin, ciprofloxacin)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





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





Mycobacterium avium Complex

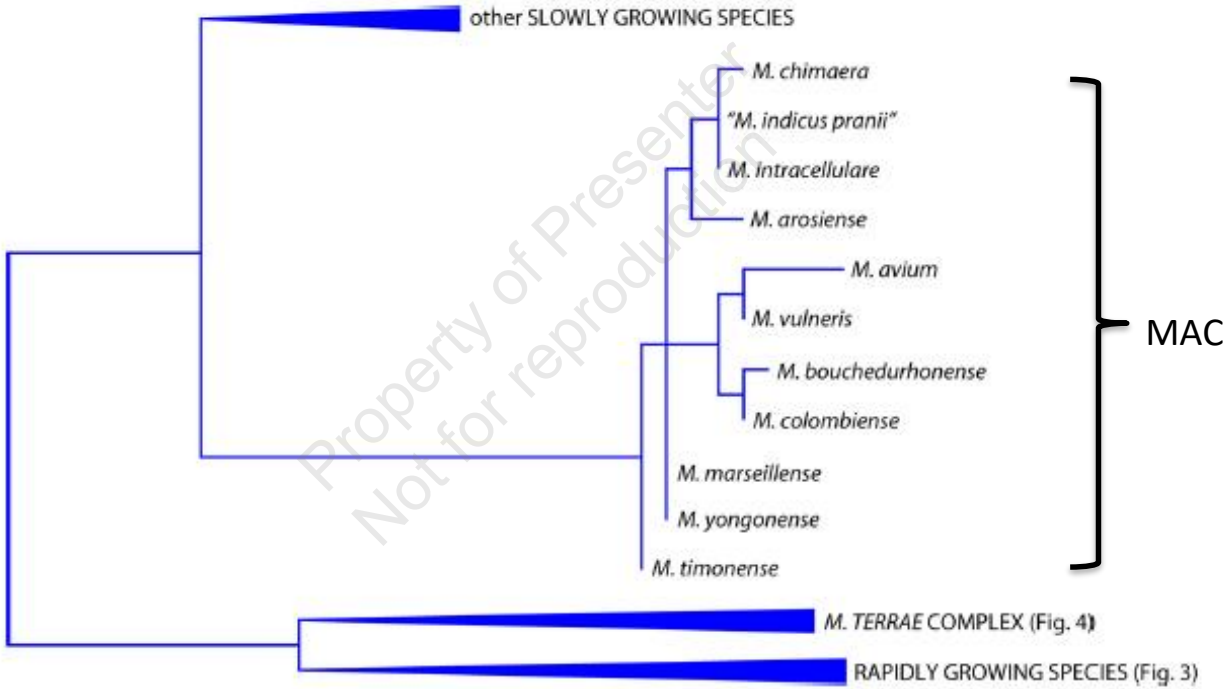


FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

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
Linezolid	32
Moxifloxacin	2
Clofazimine	0.25

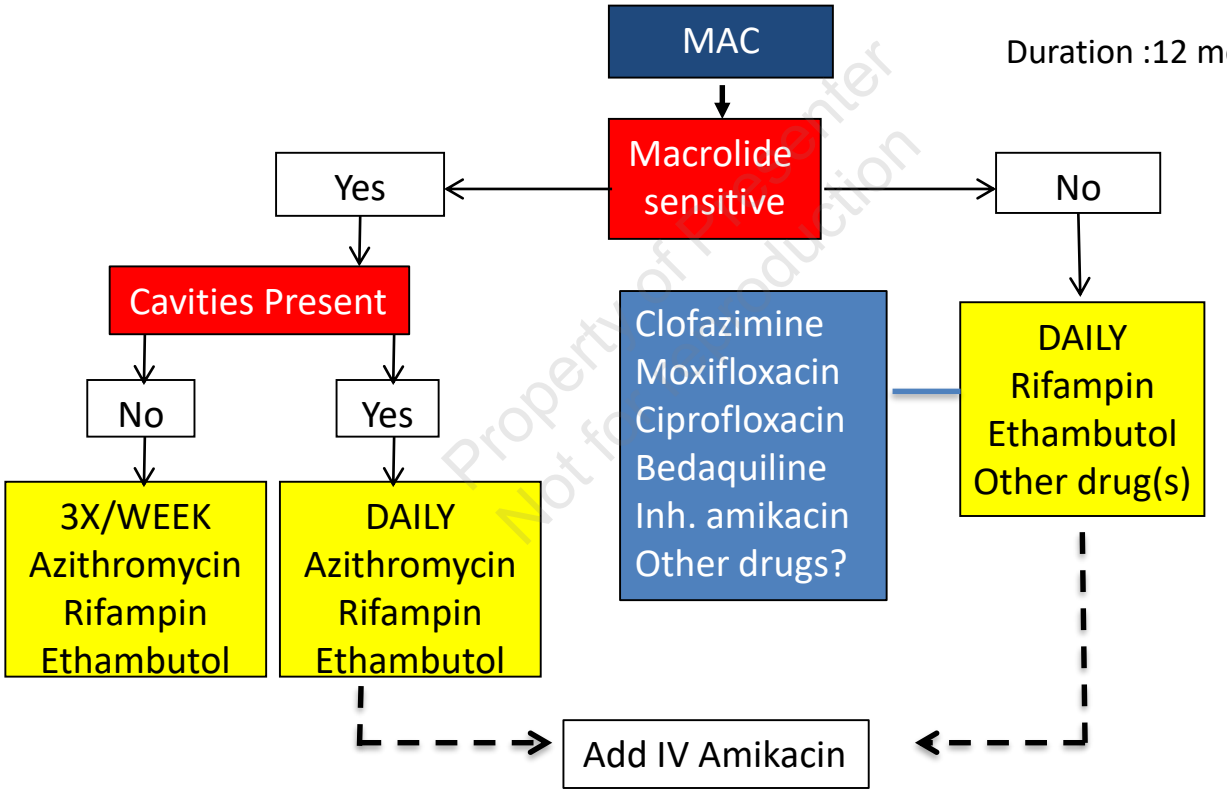
Recommended Initial Treatment Regimens for MAC Pulmonary Disease

	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

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

Treatment of Pulmonary *M. avium* complex



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

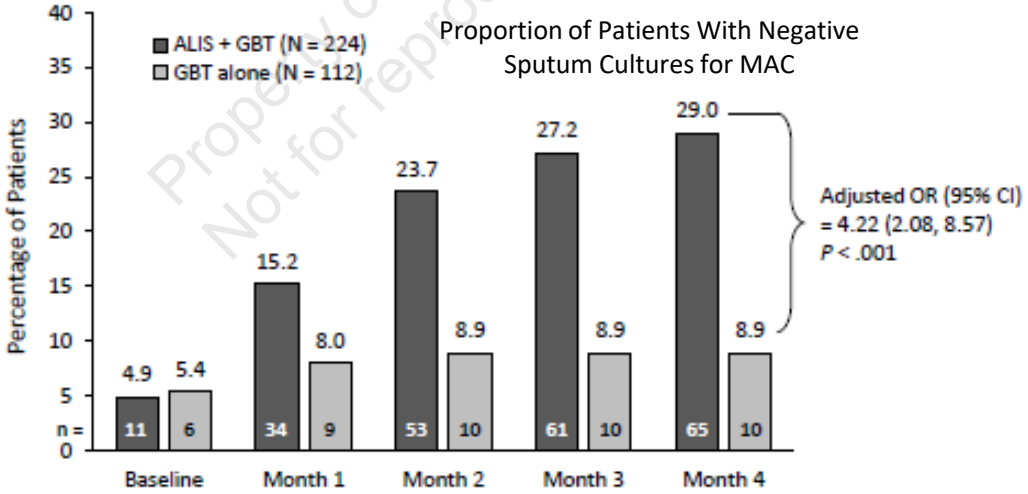
Griffith DE et al. *Am J Respir Crit Care Med.* 2006;174:928-934.
Jeong BH et al. *Am J Respir Crit Care Med.* 2015;191:96-103.
Moon SM et al. *Eur Respir J.* 2016;50:1602503.
Wallace R et al. *Chest.* 2014;146:276-282.
Koh WJ et al. *Eur Respir J.* 2017;50.
Morimoto K et al. *Ann Am Thorac Soc.* 2016;11:1904.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

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

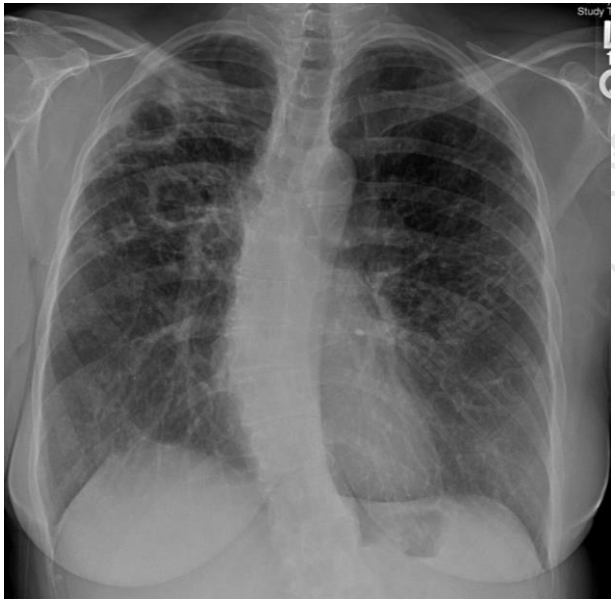
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

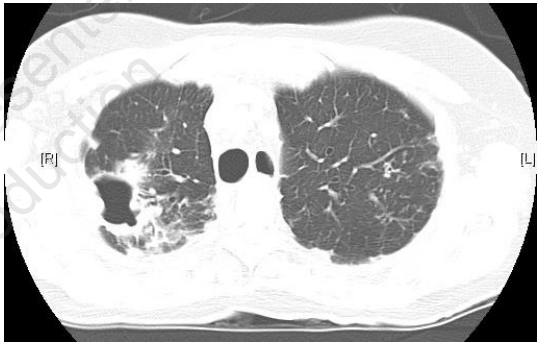
M. avium complex

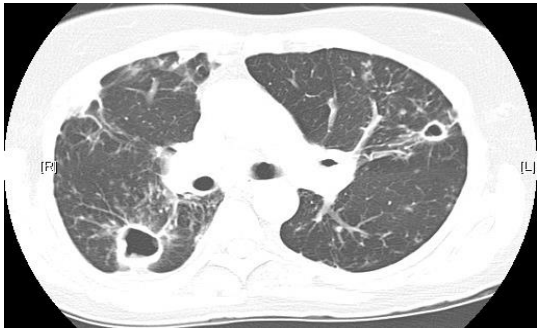
Summary

- 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
- 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)

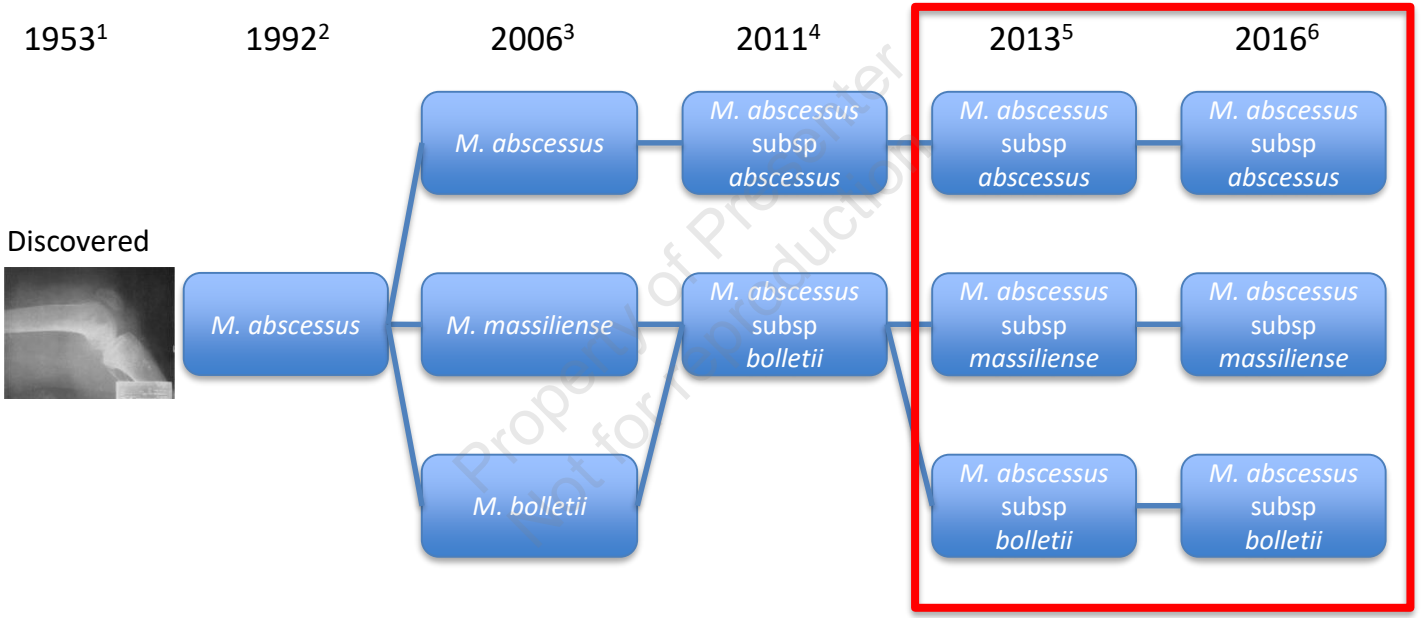
- 68 year old woman with chronic cough and fatigue







Mycobacterium abscessus: An Evolving Taxonomy

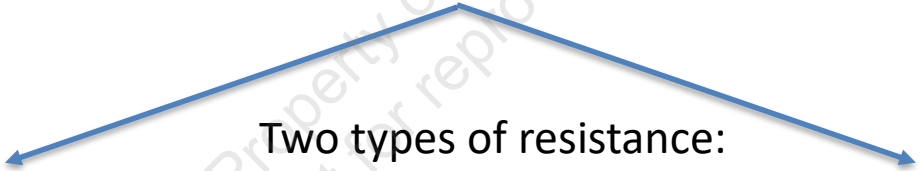


[1]Moore M J Invest Derm 1953;20:133
[2]Kusunoki S. Int J Syst Bacteriol 1992;42:240
[3]Adekambi T. Int J Syst Bacteriol 2006;56:133
[3]Adekambi T. Int J Syst Bacteriol 2006;56:2025
[4]Leao SC. Int J Syst Evol Microbiol 2011;61:2311
[5]Cho YJ. PLoS ONE 2013 8(11):e81560
[6]Tortoli E. Int J Syst Evol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



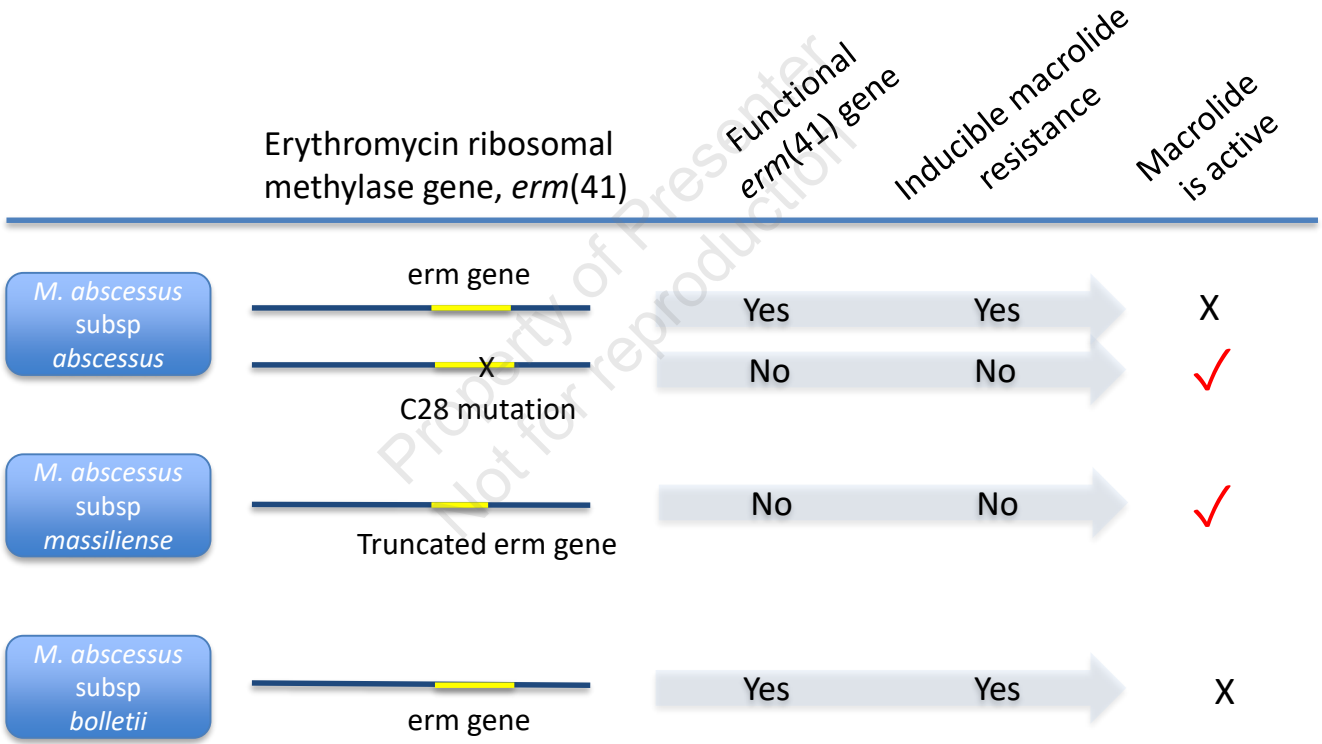
Mutational Resistance

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

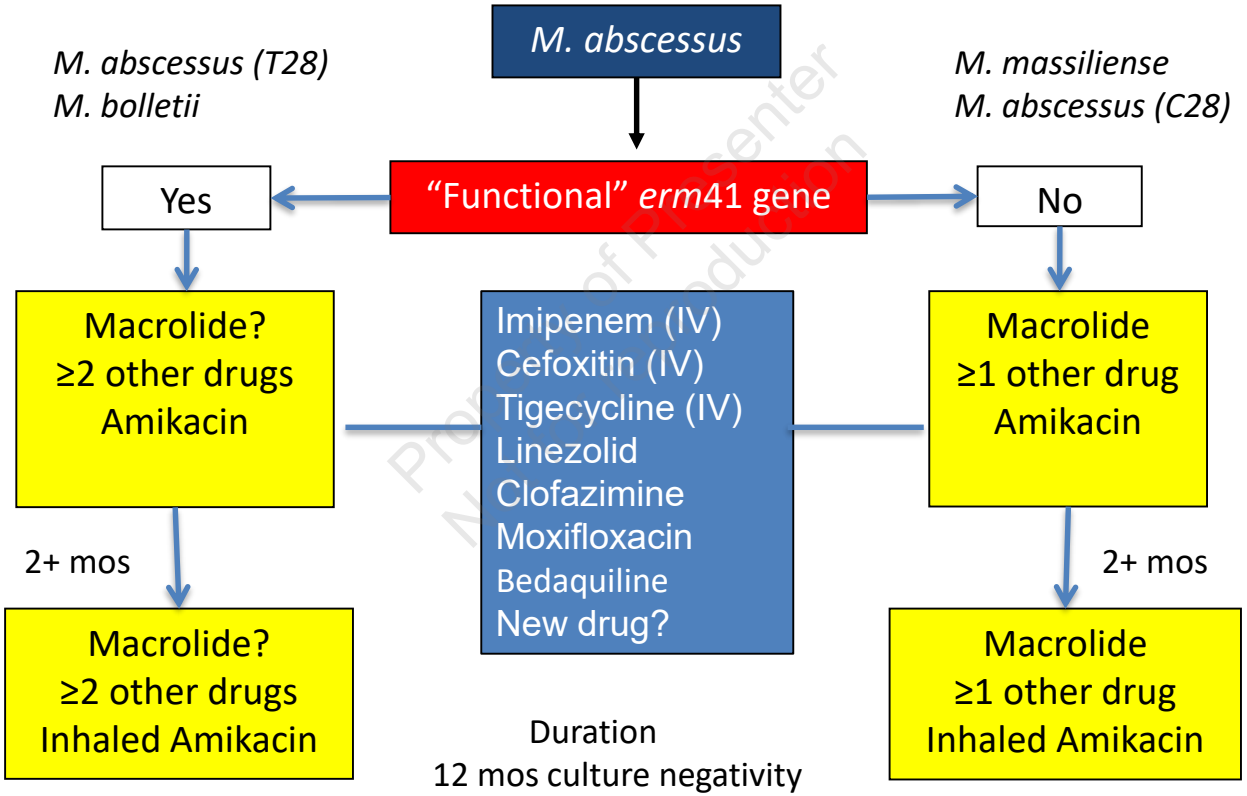
Preferred Report

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

erm(41) – present, T28 mutation

Drug susceptibility:	**MIC**
Amikacin	8
Cefoxitin	16
Clarithromycin	1
Imipenem	
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	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

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

Thank You!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Saint Joseph Hospital
Our new Center for Outpatient Health expands patient care on main campus