Nontuberculous Mycobacterial Infections

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Disclosures

Consultant: Genentech, Pfizer

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

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

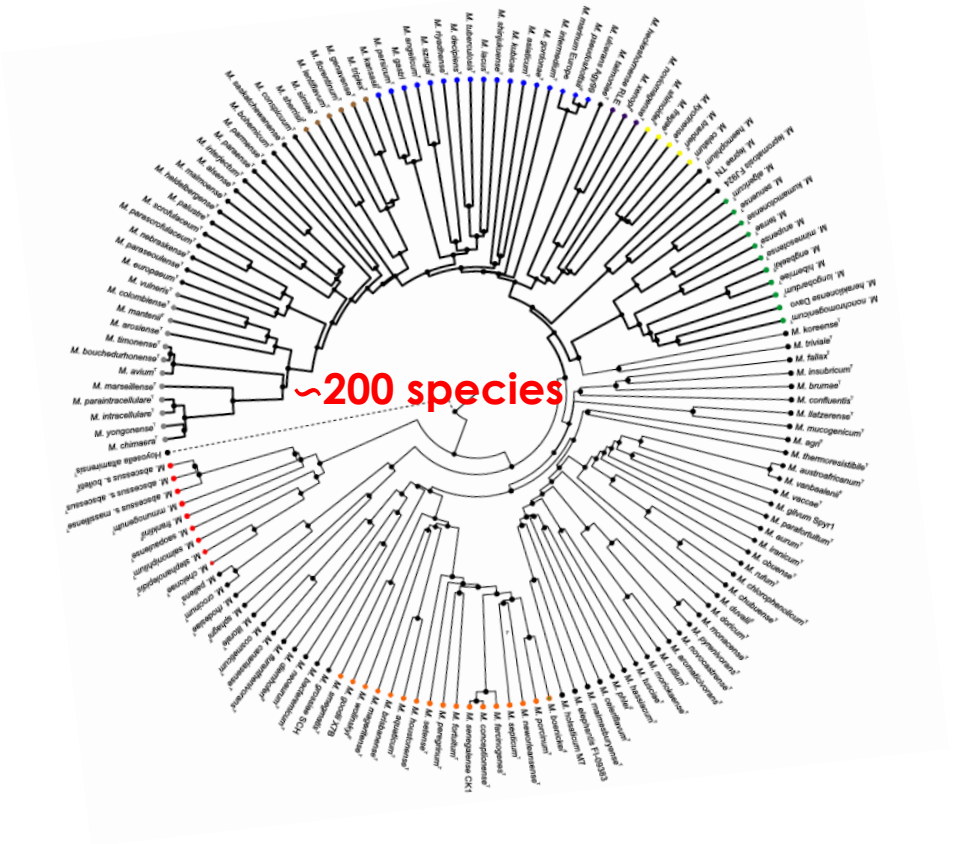
Contracted Research: AN2 Therapeutics, Bugworks, Insmed, Juvabis, Pharmaceuticals

Learning Objectives – at the end of this talk participants should be able to:

- Understand the epidemiology and clinical manifestations of NTM-PD, as well as risk factors for the disease
- Explain guideline-based diagnostic criteria and importance of the laboratory in the diagnosis of NTM-PD
- Describe current guideline-based treatment regimens for MAC-PD, including refractory disease and *M. abscessus*
- Review new and repurposed drugs in the drug development pipeline

Nontuberculous Mycobacteria (NTM)

- Environmental bacteria
- Found in soil and water
- Produce both pulmonary and extrapulmonary disease
- Pathogenicity varies greatly
- High levels of in vitro resistance
- Treatment is complex and associated with suboptimal outcomes



Tortoli E, et al. Inf Gen Evol 2017;56:19

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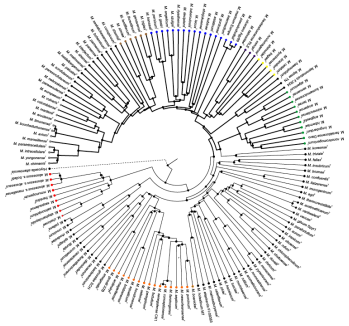
Division of Genus *Mycobacterium* into Emended Genus *Mycobacterium* and Four Novel Genera

Mycobacterium



- Mycobacteroides "*Abscessus-Chelonae*"
- Mycolicibacterium "*Fortuitum-Vaccae*"
- Mycolicibacter "*Terrae*"
- Mycolicibacillus "*Triviale*"
- Mycobacterium "*Tuberculosis-Simiae*"

Rapid Growers

Slow Growers

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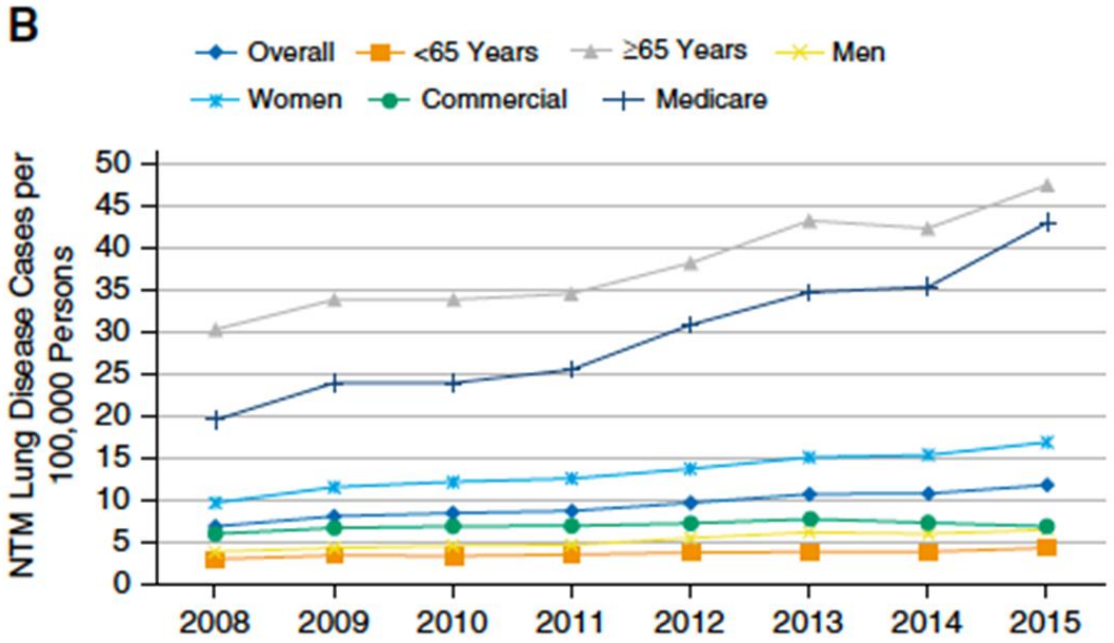
Gupta RS, et al. Frontiers Microbiol 2018;9:Art 67

Nontuberculous Mycobacteria (NTM) High Prevalence of NTM-PD and Increasing

- NTM prevalence is highest in older ages and women
- NTM prevalence is higher than TB in many countries
- Bronchiectasis is the greatest risk factor for NTM pulmonary disease
- NTM pulmonary disease is increasing in prevalence in many areas

National Managed Care Claims Database – 27 million people annually

Prevalence (per 100,000)



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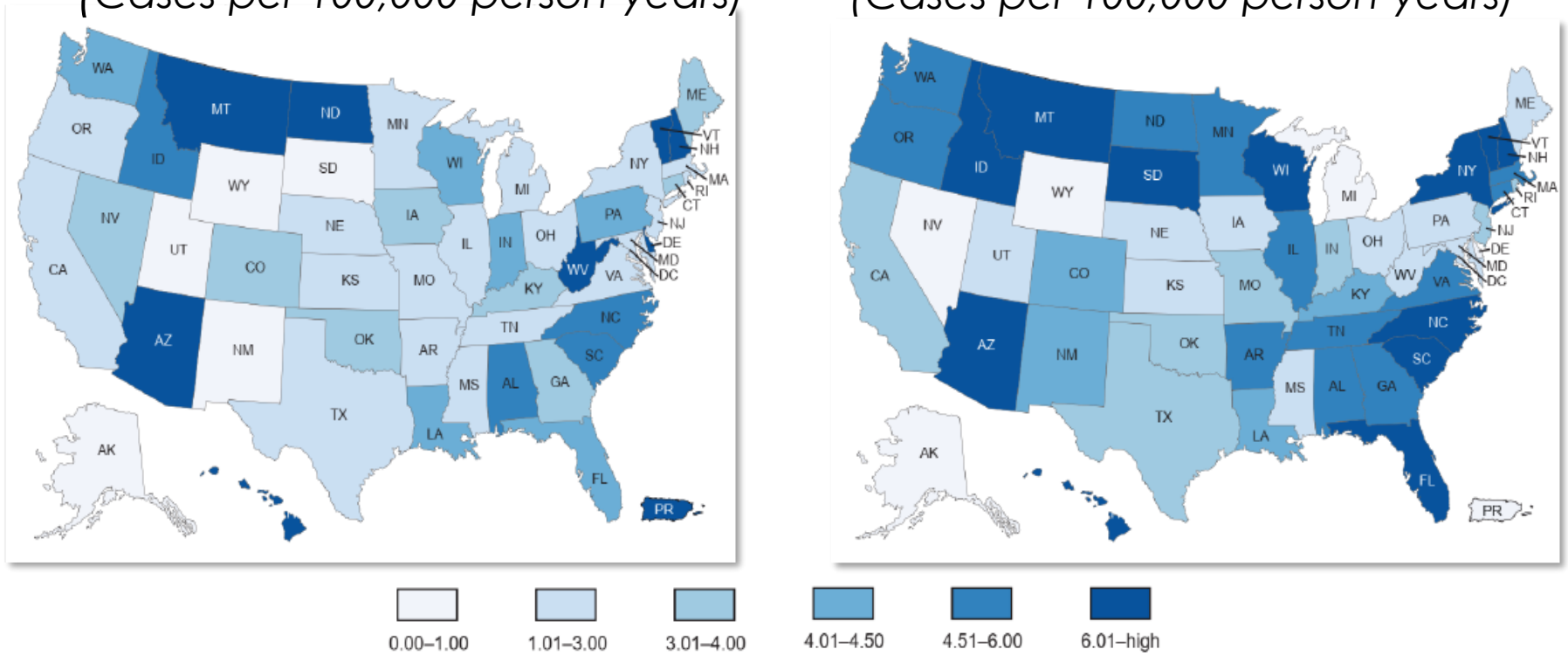
Winthrop KL, et al. *Ann Am Thorac Soc*. 2020;17(2):178-185.

Increasing NTM US Incidence, 2008-2015

NTM INCIDENCE, 2008
(Cases per 100,000 person-years)

NTM INCIDENCE, 2015
(Cases per 100,000 person-years)



Winthrop KL, et al. *Ann Am Thorac Soc*. 2020;17(2):178-185.

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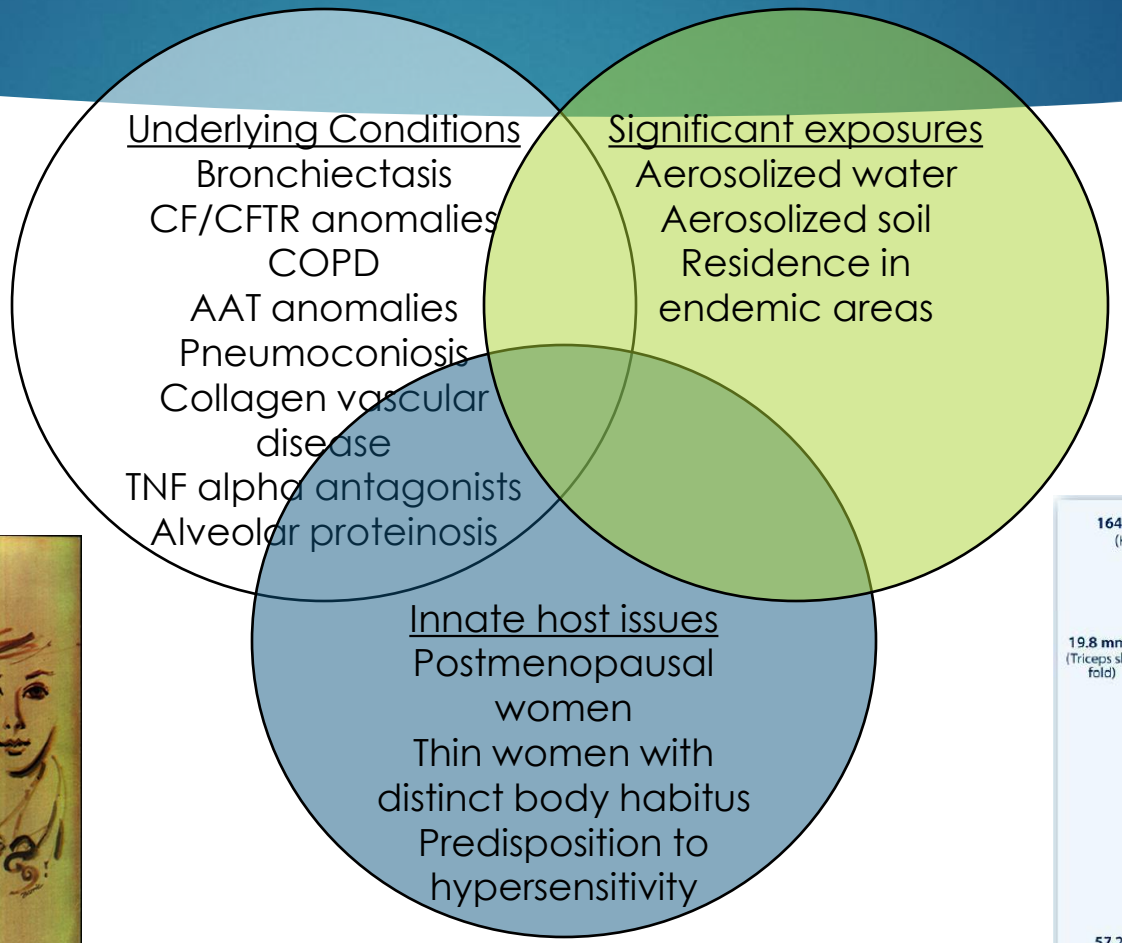
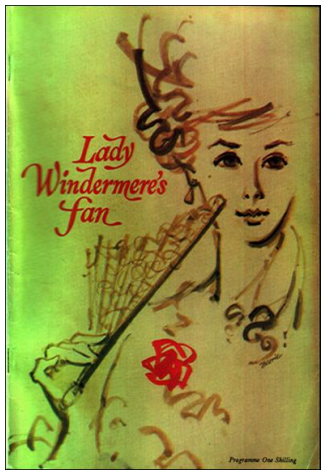
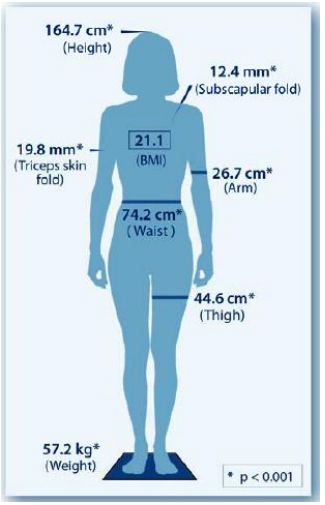
The Host - Risk Factors for NTM Infection







Chan E and Iseman MD. Gender Med 2010;7:5-18
Kim, et al. AJRCCM 2008;178:1066

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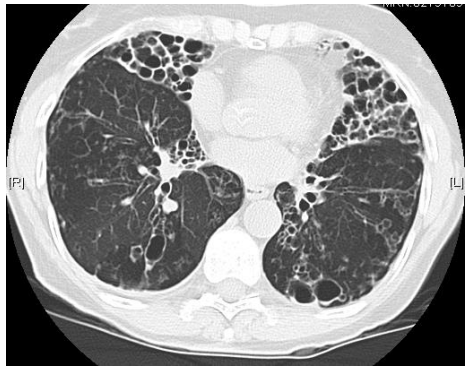
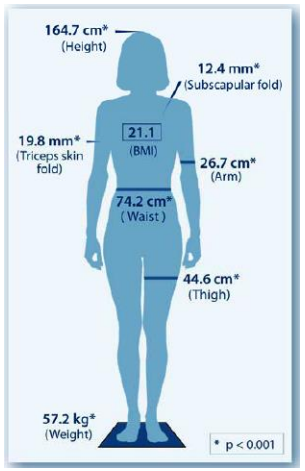
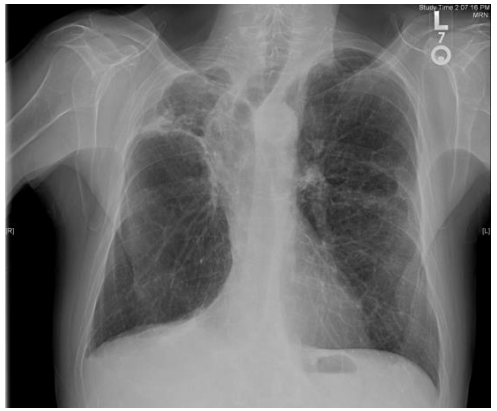
Clinical Phenotypes

- **Nodular / bronchiectatic disease**
  - Women
  - Older
  - Nonsmokers
  - Tall, thin, low body mass index





- **Fibrocavitary disease**
  - Male
  - Older
  - Smokers
  - Various body builds



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Kim RD, et al. AJRCCM 2008;178:1066-1074

Specimen Collection

Bronchoscopy specimens

- Not as good as you think
  - Lidocaine is bacteriostatic
  - Specimen is dilute
  - Sampling error
  - Unable to determine bacterial load
  - Risks
  - Costs

Sputum

- Better than you think
  - Multiple specimens – 3 over at least one week, preferably over weeks
  - Sputum AFB smear positivity and number of cultures are associated with progression of NTM disease
  - Similar culture yield as bronchoscopy in TB and NTM*
  - Induction with hypertonic saline is easy! Patients can do it at home

* Ikeda Y. Kurume Med J. 2001;48:15-9.

NTM Pulmonary Disease: Diagnostic Criteria

Clinical	Pulmonary or Systemic Symptoms	Both required
Radiological	Nodular or cavitary opacities on chest radiograph or HRCT that shows bronchiectasis with multiple small nodules	
Appropriate exclusion of other diagnoses		
Microbiological	1. Positive cultures from at least **two** separate sputum samples. If the results are nondiagnostic, consider repeat repeat sputum AFB smears and cultures **or** 2. Positive cultures 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	

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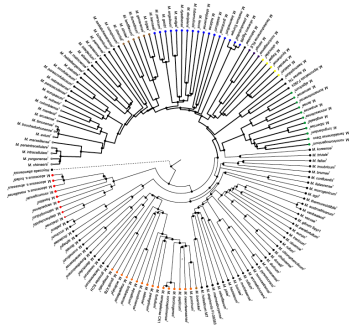
Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Diagnosis of NTM Infections: Laboratory Diagnosis

Drug susceptibility

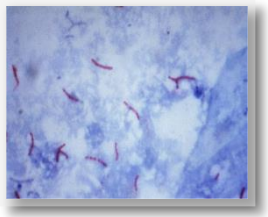


Identification

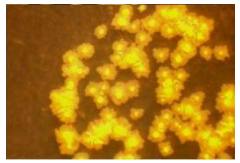
Think about it!

Diagnosis
8 weeks

Collect a specimen



Microscopic examination



Culture (liquid and solid media)

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Antimicrobial Susceptibility Testing

Species	Drugs
M. kansasii	Rifampicin Clarithromycin*
MAC	Macrolide Amikacin
M. abscessus	Macrolide (including *erm*(41) gene) Amikacin

AST for MAC

Antimicrobial Agent	MIC, ug/ml		
	S	I	R
Clarithromycin	≤ 8	16	≥ 32
Amikacin (IV)	≤ 16	32	≥64
Amikacin (liposomal inhaled)	≤ 64	-	≥ 128

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*CLSI. M62 Performance Standards for Susceptibility Testing, 2018

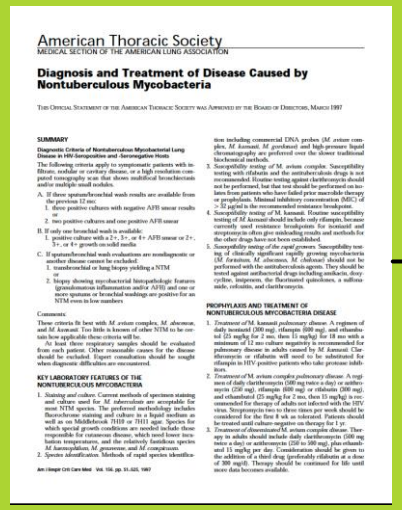
Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Multi-society NTM Treatment Guidelines

1990

DIAGNOSIS AND TREATMENT OF DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA

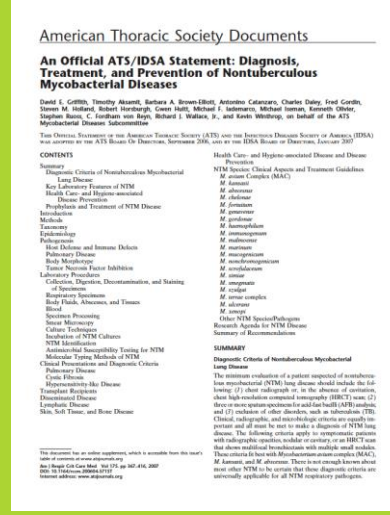
1997



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

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

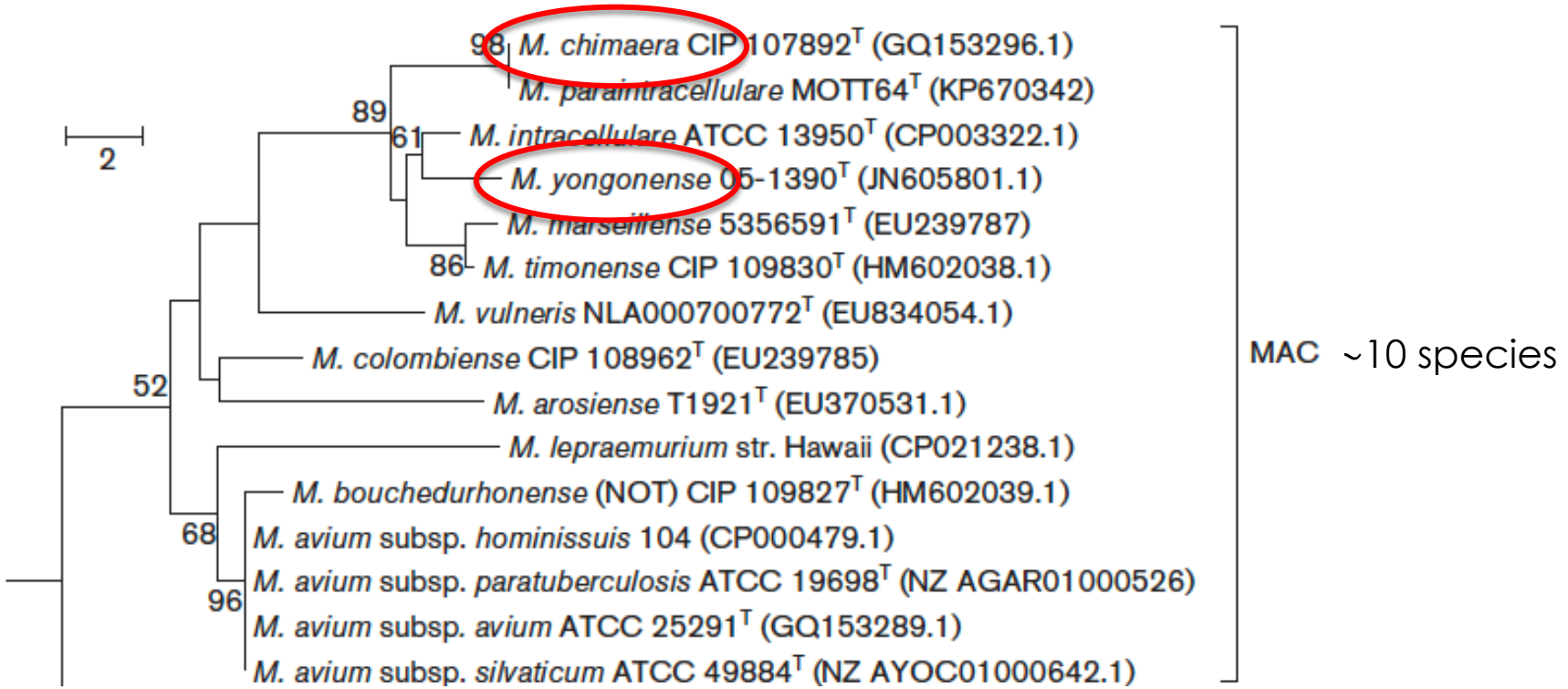
2022

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

Mycobacterium avium complex - the most common NTM pulmonary pathogen



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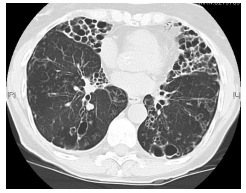
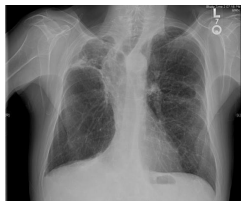
Van Ingen J, et al. Int J Syst Evol Microbiol. 2018, Vol.68(11), p.3666-3677.

Recommended Initial Treatment Regimens for Drug Susceptible MAC Pulmonary Disease





	No. of Drugs	Preferred Regimen[a]	Dosing Frequency	Duration
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly	12 months beyond culture conversion
Cavitary	≥ 3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (IV aminoglycoside may be used 3 times weekly)	

a. Alternative drugs could include clofazimine, fluoroquinolones, 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

Initiate Treatment or ”Watchful Waiting”?

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

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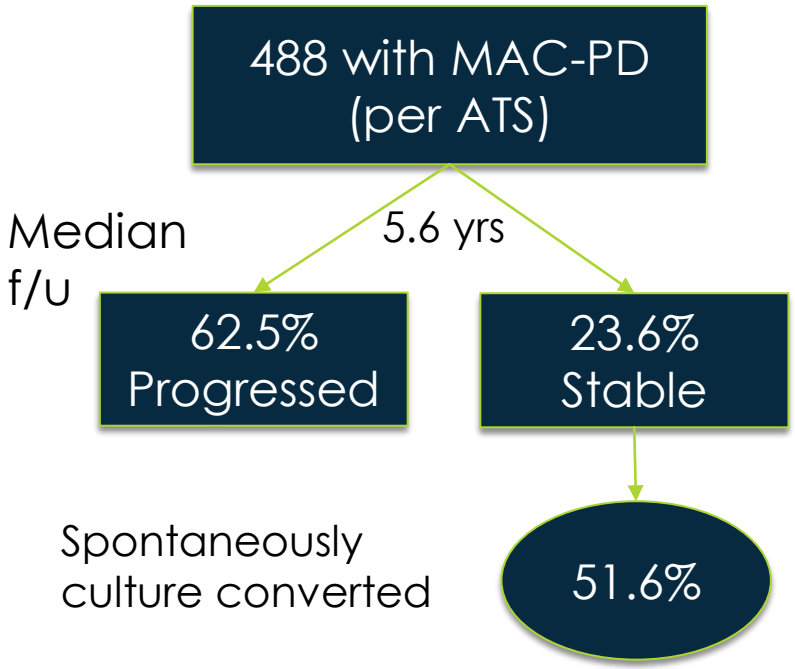

Hwang JA, et al.
Eur Respir J 2017;49:1600537

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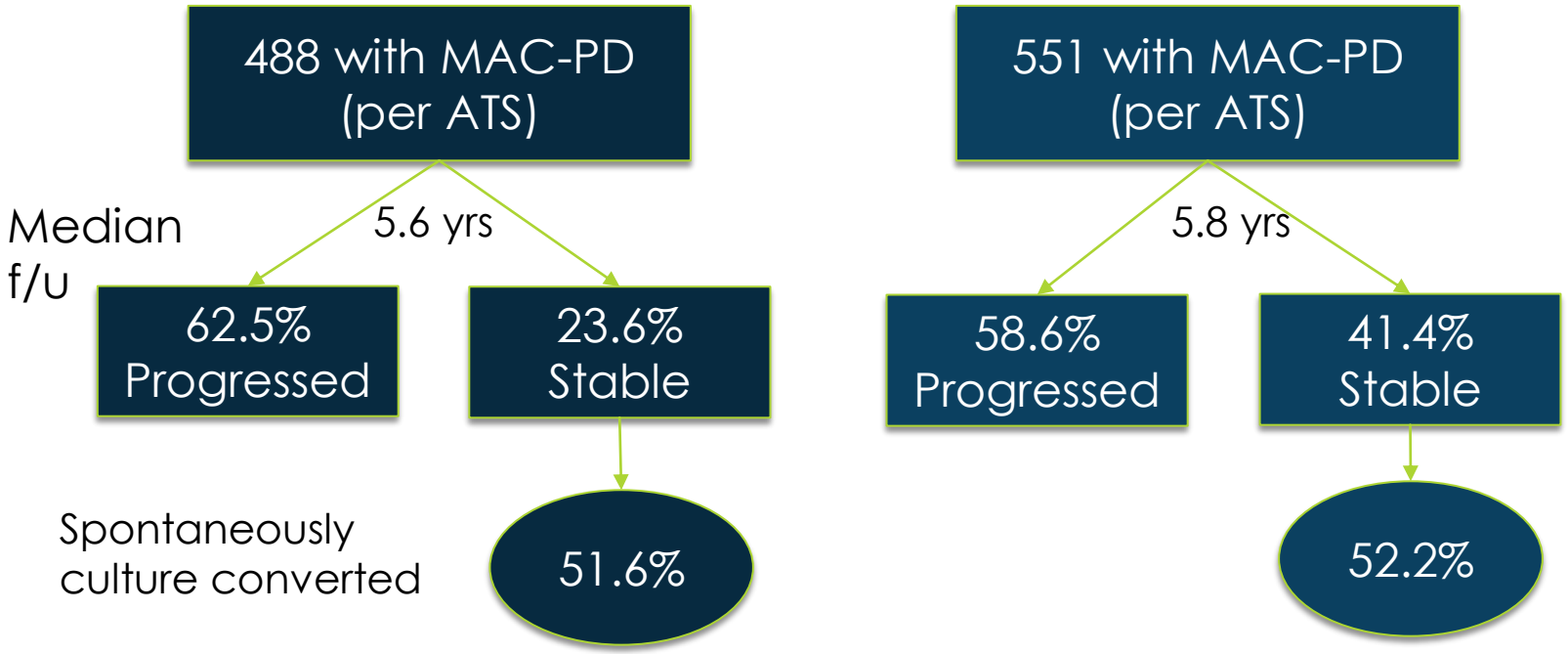

Hwang JA, et al.
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Resp Med 2019;150:45-50

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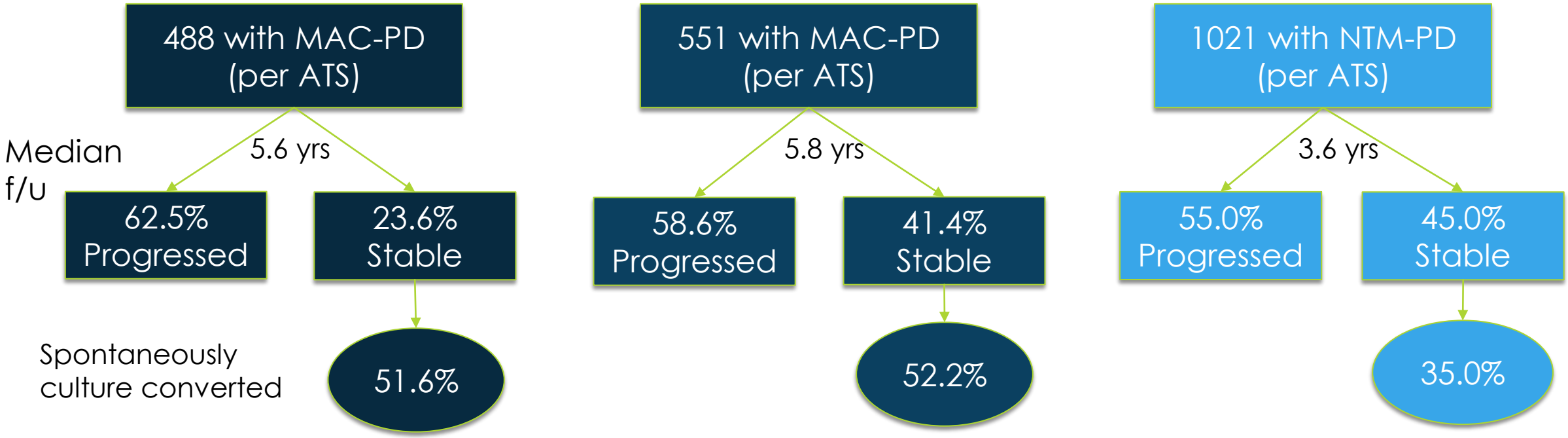

Hwang JA, et al.
Eur Respir J 2017;49:1600537

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

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

Risk Factors Associated with Progression

Host/Demographic Factors	Laboratory Factors	Radiographic Factors	Microbial Factors
• Male gender • Older age • Presence of co-morbidities • Low body mass index	• Elevated inflammatory indices (ESR, CRP) • Anemia • Hypoalbuminemia	• Fibrocavitary • Extent of disease	• Bacterial load • Species

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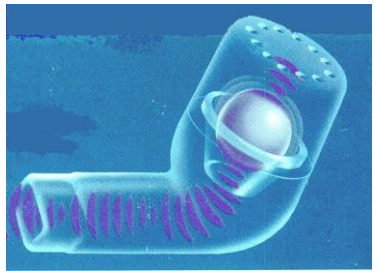
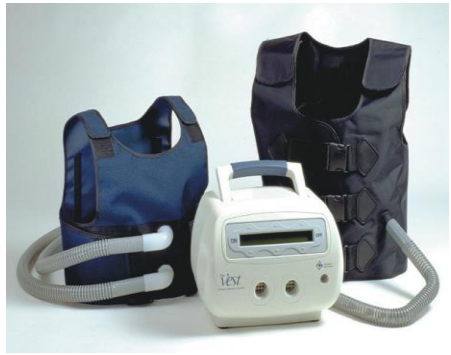
Hwang JA, et al. Eur Respir J 2017;49:1600537
Kwon BS, et al. Resp Med 2019;150:45-50
Moon SM, et al. Resp Med 2019;151:1-7.

Nonpharmacologic Therapy

- **Airway Clearance**
  - Regular exercise
  - Vibratory PEP
  - Chest percussion
  - Nebulized hypertonic saline
  - Chest wall oscillation
- **Pulmonary rehabilitation**
- **Nutrition**
- **GERD**
  - Lifestyle modifications



Best choice is what the patient will do

- Education
- Time commitment

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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%
Macrolide resistant			
No surgery/aminoglycoside* Some surgery/aminoglycoside Surgery + prolonged aminoglycoside*	5% 15% 80%	–	–

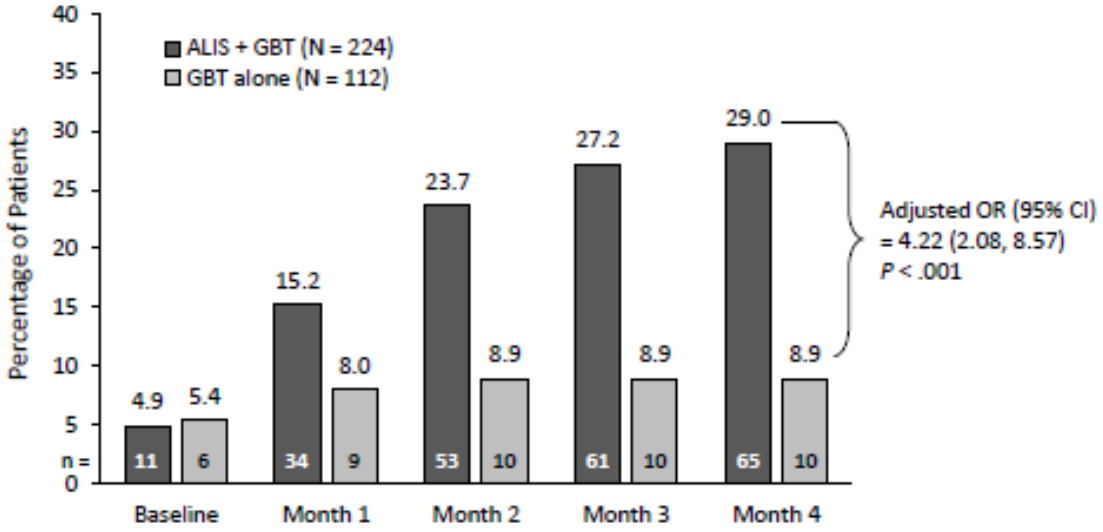
Griffith DE et al. *Am J Respir Crit Care Med.* 2006;174:928-934.
Jeong BH et al. *Am J Respir Crit Care Med.* 2015;191:96-103.
Moon SM et al. *Eur Respir J.* 2016;50:1602503.
Wallace R et al. *Chest.* 2014;146:276-282.
Koh WJ et al. *Eur Respir J.* 2017;50.
Morimoto K et al. *Ann Am Thorac Soc.* 2016;11:1904.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

Treatment Refractory MAC Pulmonary Disease Inhaled Amikacin

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



Proportion of Patients With Negative Sputum Cultures for MAC

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

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

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

Sustainability and Durability of Culture Conversion

In patients who achieved culture conversion by month 6 in CONVERT:

- Was conversion **sustained** (negative results for 12 mos on treatment)
- Was conversion **durable** (negative results for 3 mos and 12 mos after treatment)

		% Remaining Culture Negative		
Condition	**Time of Measurement**	**ALIS +GBT**	**GBT**	**P-value**
Sustained	**12 months on therapy**	**63.1%**	**30.0%**	**0.064**
Durable	**3 months after therapy**	**55.4%**	**0%**	**0.0017**
	12 months after therapy	**46.2%**	**0%**	**< 0.0001**

Griffith D, et al. *Chest* 2021;160:831-842

Recommended Treatment Regimens for Treatment Refractory MAC Pulmonary Disease

- Switching from intermittent therapy to daily therapy
- Adding additional medications
  - Amikacin liposome inhalation suspension
  - Clofazimine
  - Bedaquiline
  - Oxazolidinones (linezolid, tedizolid)
  - Flouroquinolones?
- Substituting medications
  - Rifabutin (substituting for rifampin)
- Surgery

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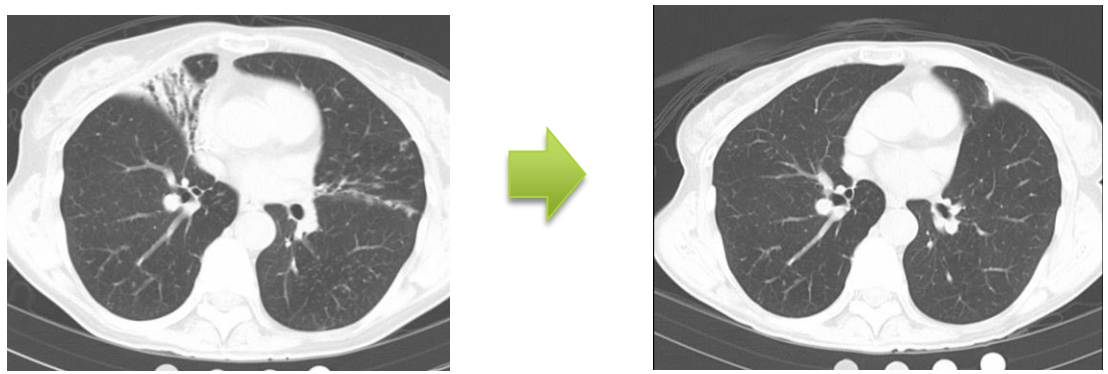
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

Surgery Plus Medical Therapy or Medical Therapy Alone?

Recommendation

In selected patients with NTM pulmonary disease, we suggest surgical resection as an adjuvant to medical therapy after expert consultation (conditional recommendation, very low certainty in estimates of effect)

- 15 observational studies including approximately 700 patients who underwent surgical resection including 3 studies (296 patients) that compared outcomes in those who had surgery plus antimicrobial therapy vs antimicrobial therapy alone
  - Culture conversion more common in those who underwent surgery
  - Complications in 7-35%
  - No operative mortality
  - 0-9% post-operative mortality
  - Beware of selection bias



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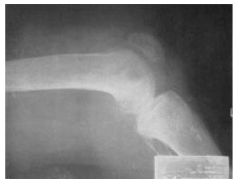
Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Mycobacterium abscessus
An Evolving Taxonomy

1953[1]	1992[2]	2006[3]	2011[4]	2013[5]	2016[6]	2018[7]	Active erm(41) gene
Discovered	*M. abscessus*	*M. abscessus*	*M. abscessus* subsp *abscessus*	*M. abscessus* subsp *abscessus*	*M. abscessus* subsp *abscessus*	*Mycobacterioides abscessus* subsp *abscessus*	
		M. massiliense	*M. abscessus* subsp *bolletii*	*M. abscessus* subsp *massiliense*	*M. abscessus* subsp *massiliense*	*Mycobacterioides abscessus* subsp *massiliense*	~0%
		M. bolletii		*M. abscessus* subsp *bolletii*	*M. abscessus* subsp *bolletii*	*Mycobacterioides abscessus* subsp *bolletii*	~100%



[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]Gupta RS, et al. Frontiers Microbiol 2018;9:Art 67

Mycobacterium abscessus: Macrolide Resistance

Resistance to macrolides impacts treatment outcomes

Two types of resistance:

Mutational Resistance

Mutation in *rrl* gene

Inducible Resistance

Erythromycin ribosomal methylase gene, *erm*(41):

- *M. abscessus* ~80-90%
- *M. massilliense* ~0%
- *M. bolletii* ~100%

Recommended Treatment Regimens
M. abscessus – A Phased Approach

Macrolide Susceptibility					
Mutational	Inducible	No. of Drugs	Preferred Drugs	Frequency of Dosing	Treatment Success
Susceptible	Susceptible	Initial Phase ≥3	*Parenteral (choose 1-2)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin* Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	> 80%
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin* Clofazimine Linezolid Inhaled amikacin		

*Azithromycin is active
**Azithromycin is unlikely to be active

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

Recommended Treatment Regimens
M. abscessus – A Phased Approach

Macrolide Susceptibility					
Mutational	Inducible	No. of Drugs	Preferred Drugs	Frequency of Dosing	Treatment Success
Susceptible	Susceptible	Initial Phase ≥3	*Parenteral (choose 1-2)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin* Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	> 80%
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin* Clofazimine Linezolid Inhaled amikacin		
Susceptible	Resistant	Initial Phase ≥ 4	*Parenteral (choose 2-3)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2-3)* Azithromycin** Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	<40%
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin** Clofazimine Linezolid Inhaled amikacin	Weak Regimen!	

*Azithromycin is active
**Azithromycin is unlikely to be active

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

Recommended Treatment Regimens
M. abscessus – A Phased Approach

Macrolide Susceptibility					
Mutational	Inducible	No. of Drugs	Preferred Drugs	Frequency of Dosing	Treatment Success
Susceptible	Susceptible	Initial Phase ≥3	*Parenteral (choose 1-2)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin* Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	> 80%
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin* Clofazimine Linezolid Inhaled amikacin		
Susceptible	Resistant	Initial Phase ≥ 4	*Parenteral (choose 2-3)* Amikacin Imipenem (or cefoxitin) Tigecycline *Oral (choose 2-3)* Azithromycin** Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	<40%
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2-3)* Azithromycin** Clofazimine Linezolid Inhaled amikacin	Weak Regimen!	
Resistant	Susceptible or Resistant	As above			<40%

*Azithromycin is active
**Azithromycin is unlikely to be active

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

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

Novel Treatments for NTM Infections

Repurposed Drugs

- Dual beta lactams ± beta-lactamase inhibitors
- Cycline derivatives
- Rifabutin (for *M. abscessus*)
- Apramycin

New Drugs

- Epetraborole
- SPR720

New Formulations

- Inhaled tigecycline
- Inhaled clofazimine

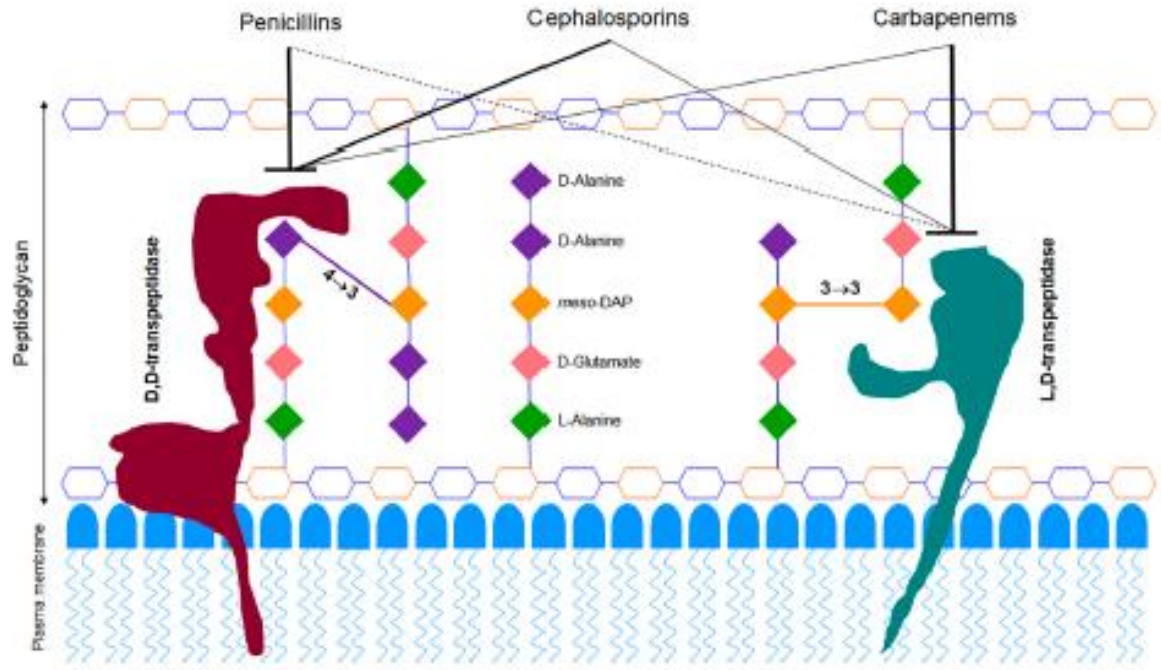
Non-antimicrobials

- Inhaled NO
- Inhaled GM-CSF
- Gallium
- Bacteriophage

Mycobacterium abscessus and β-lactamase Inhibitors

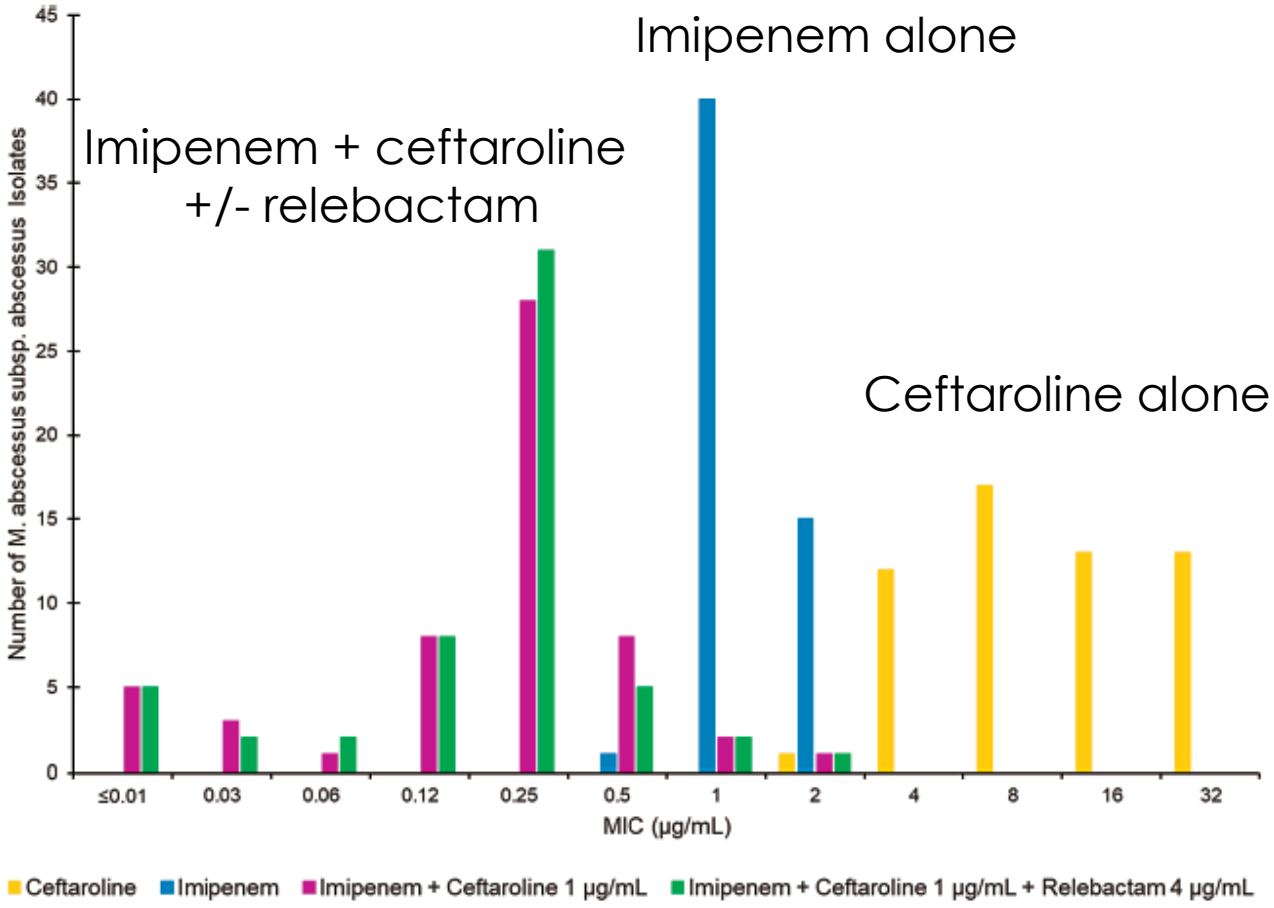
- *Mycobacterium abscessus* produces a broad spectrum β-lactamase (Bla_{Mab})
  - Imipenem and cefoxitin are slowly hydrolyzed by Bla_{Mab} which contributes to their efficacy
- Inhibition of Bla_{Mab} by avibactam improves the efficacy of imipenem against *M. abscessus in vitro*, in macrophages and zebrafish embryos
- Combinations of beta-lactams have shown synergistic activity against *M. abscessus* in vitro and in mouse models

Model of *M. abscessus* Peptidoglycan



Lefebvre AL, et al. Antimicrob Agents Chemother 2017 epub
Dubee V, et al. Antimicrob Agents Chemother 2015;59:2938
Story-Roller E, et al. Antimicrob Agents and Chemother 2019;63:e02613-18

In vitro Activity Imipenem, Ceftaroline and Combination



- Imipenem and ceftaroline bind the same targets in peptidoglycan synthesis
  - Imipenem preferentially binds the transpeptidases and likely improves binding of ceftaroline
- Addition of relebactam did not increase activity beyond the combinations of the two beta-lactams

Dousa K, et al. Antimicrob Agents Chemo. 2020;64:e00098-02
Nguyen DC, et al. Clin Infect Dis 2021;73:1532-6

Cycline Derivatives

- Tigecycline has good activity against *M. abscessus* but is associated with high rates of nausea/vomiting (30-50%)
- Omadacycline is a newer cycline that comes in both oral and IV preparations and was approved by the US FDA for treatment of community-acquired bacterial pneumonia and skin infections in 2018
- Compared with tigecycline, nausea/vomiting are less frequent
  - nausea/vomiting occurred in 15%/8% of patients with the IV form and 25%/12% with oral dose
  - Much of the nausea/vomiting with the oral dose occurred during the loading dose that would not be necessary when treating NTM

Opal S, et al. Clin Infect Dis 2019;69:S40-S47

In vitro Activity of Omadacycline, Tigecycline, and Eravacycline

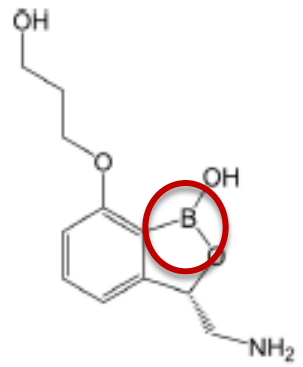
			Omadacycline		Tigecycline		Eravacycline	
Study	No. Isolates	Subpecies	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Shoen, et al	24	M. abscessus	1	2	1	2	-	-
Kaushik, et al	16	M. abscessus	2	4	1	2	0.5	1
	12	M. massiliense	1	2	1	2		
Brown-Elliott, et al	20	M. abscessus	0.12	0.25	0.12	0.25	-	-
	3	M. massiliense	0.12		0.25			

Shoen C, et al. Antimicrob Agents Chemother 2019;63:e02522-18
Kaushik A, et al. Antimicrob Agents Chemother 2019;63:e00470-19
Brown-Elliott B, et al. Antimicrob Agents Chemother 2021;65:e01947-20

Omadacycline *M. abscessus* Case Series

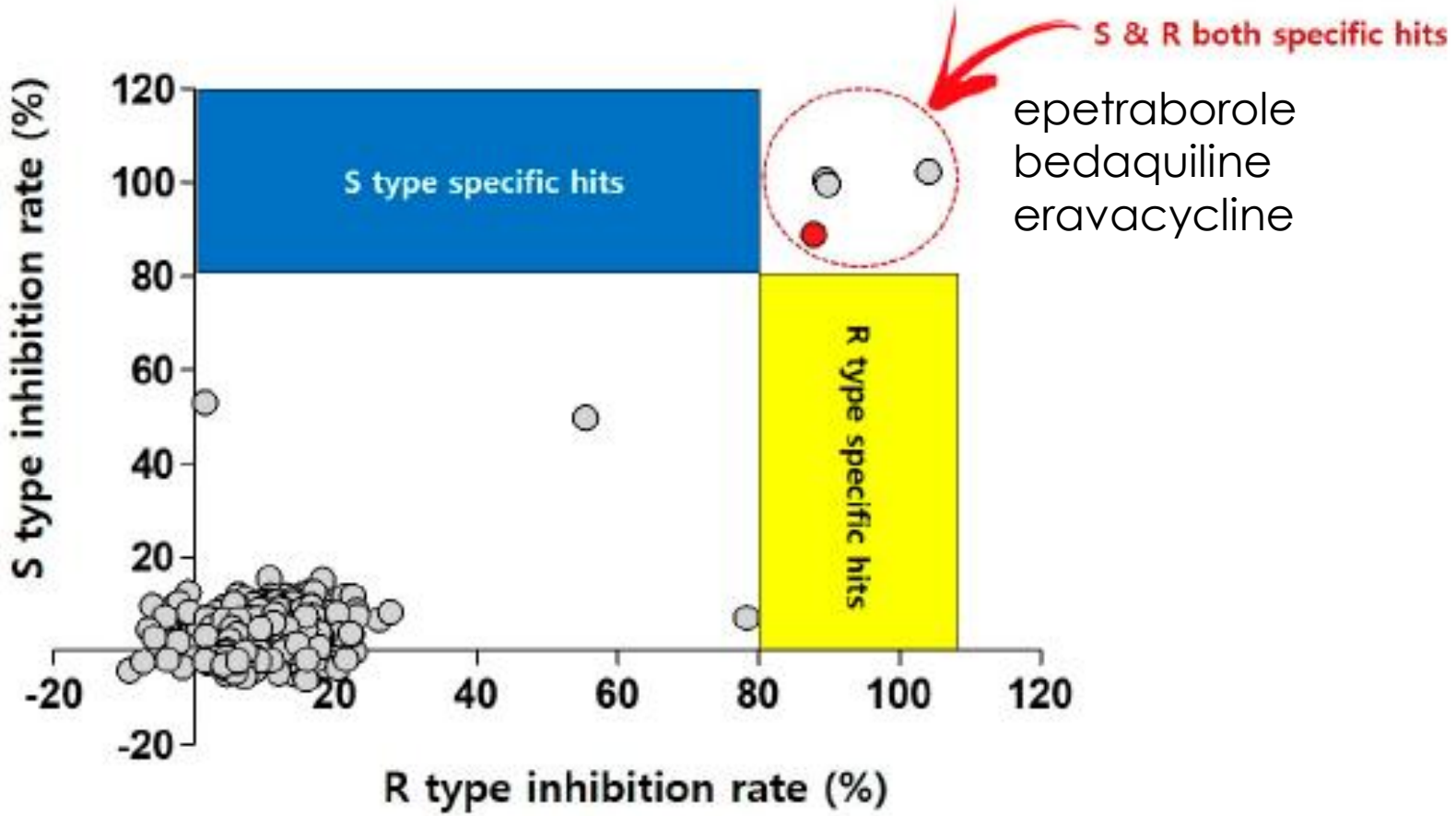
Study (date)	N	Site of Infection	Companion Drugs	AEs Due to Omadacycline	Outcome
Pearson (2020)	4	Pulmonary (1) XPulm (3)	1-3 drugs	N/V (1)	75% Cured
Morrisette (2021)	12	Pulmonary (7) Xpulm (5)	2-3 drugs	GI (1) Increased Cr (1) Increased AST/ALT	75% clinical success
Duah (2022)	3	Pulmonary (3)	2 drugs	N/V (1)	100% clinical success 2/3 culture negative
Sidddiqa (2023)	5	Pulmonary (1) Xpulm (4)	2-3 drugs	?	100% clinical success
Mingora (2023	117	Under review			

Activity of Epetraborole in *M. abscessus*



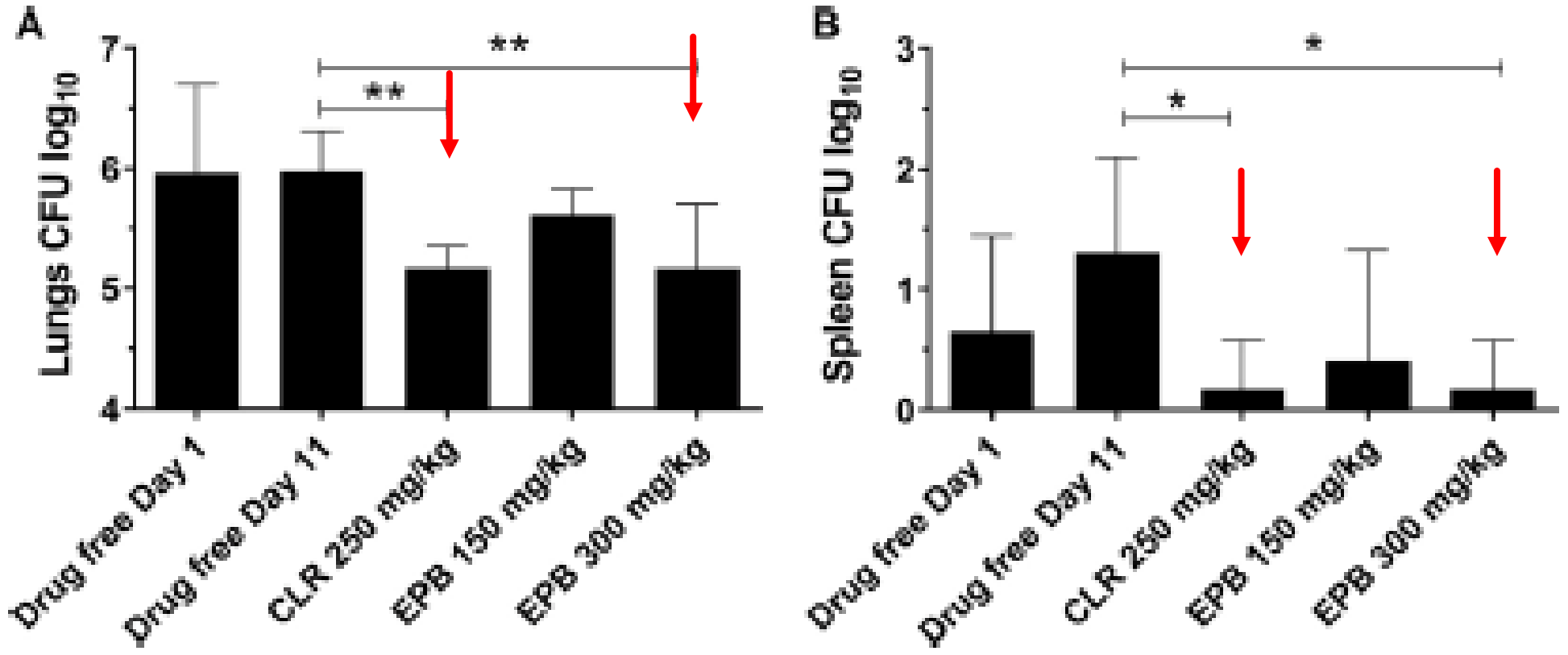
Epetraborole

Pandemic Response Box: Library contains 400 structurally diverse compounds (201 antibacterials, 153 antivirals, and 46 antifungals) for screening against infective and neglected diseases.



Kim T, et al. Int J M Sci 2021;22:5936

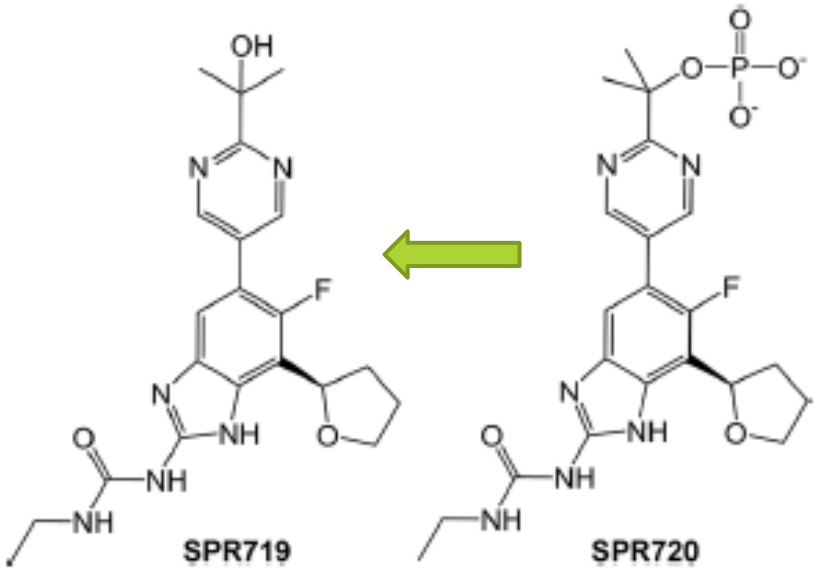
Epetraborole Has Similar In Vitro Activity as Clarithromycin Against *M. abscessus*



Dick T, et al. Antimicrob Agents Chemother 2021:65:e01156

SPR720/SPR719

- SPR720 is an aminobenzimidazole, gyrase B inhibitor that is converted to SPR719 which is the active moiety
- In vitro, mouse model, and hollow fiber models have demonstrated activity against slowly growing NTM like MAC and *M. kansasii*
- The drug is formulated for oral administration
- Phase 1 study: well tolerated over 14 days, no SAEs



Talley AK, et al. Antimicrob Agents Chemother 2021;65:e01208-21
Aragaw WW, et al. Micro Spectrum 2022;10:e01321-21

Activity of SPR719 Against NTM

NTM species	MIC range (mg/liter)	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
MAC ($n = 73$)	0.06–4	1	2
M. kansasii ($n = 21$)	<0.03–0.25	<0.03	0.125
M. abscessus ($n = 32$)	1 to >32	2	8
M. simiae ($n = 4$)	2–8	NA	NA
M. malmoense ($n = 3$)	0.06–0.5	NA	NA
M. xenopi ($n = 5$)	0.06–0.5	NA	NA

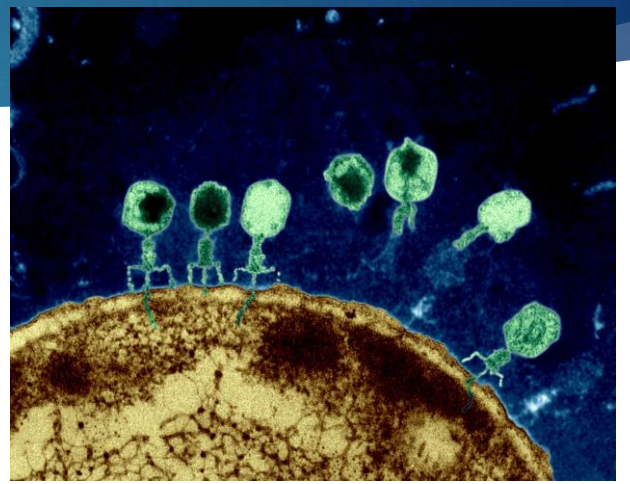
[a]MAC, *M. avium* complex; NA, not applicable.

- Bacteriostatic activity against MAC and synergy with ethambutol
- Bactericidal activity against *M. kansasii*

Pennings LJ, et al. Antimicrob Agents Chemother 2021;65:e02469-02

Bacteriophage

- Bacteriophage - Virus that infect bacteria
- Phages are the most abundant organisms in the biosphere - 10^{31} phage with entire population turning over every few days
- Genomically, small, old and diverse
- Anecdotal reports of successful treatment for resistant microbes



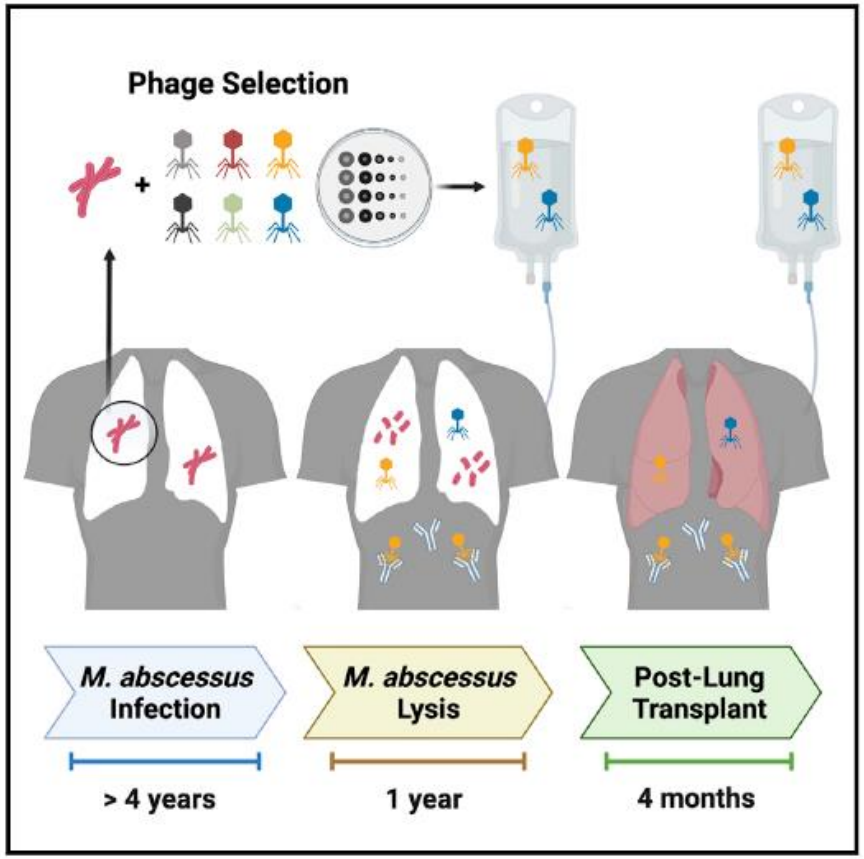
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

Robert T. Schooley,[a] Biswajit Biswas,[b,c] Jason J. Gill,[d,e] Adriana Hernandez-Morales,[f] Jacob Lancaster,[a] Lauren Lessor,[a] Jeremy J. Barr,[g,o] Sharon L. Reed,[a,h] Forest Rohwer,[g] Sean Benler,[g] Anca M. Segall,[g] Randy Taplitz,[a] Davey M. Smith,[a] Kim Kerr,[a] Monika Kumaraswamy,[a] Victor Nizet,[i,j] Leo Lin,[i] Melanie D. McCauley,[a] Steffanie A. Strathdee,[a] Constance A. Benson,[a] Robert K. Pope,[k] Brian M. Leroux,[k] Andrew C. Picel,[l] Alfred J. Mateczun,[b] Katherine E. Ciliwa,[n] James M. Regeimbal,[b] Luis A. Estrella,[b] David M. Wolfe,[b] Matthew S. Henry,[b,c] Javier Quinones,[b,c] Scott Salka,[m] Kimberly A. Bishop-Lilly,[b,c] Ry Young,[e,f] Theron Hamilton[b]

Mycobacteriophage Therapy for *M. abscessus*

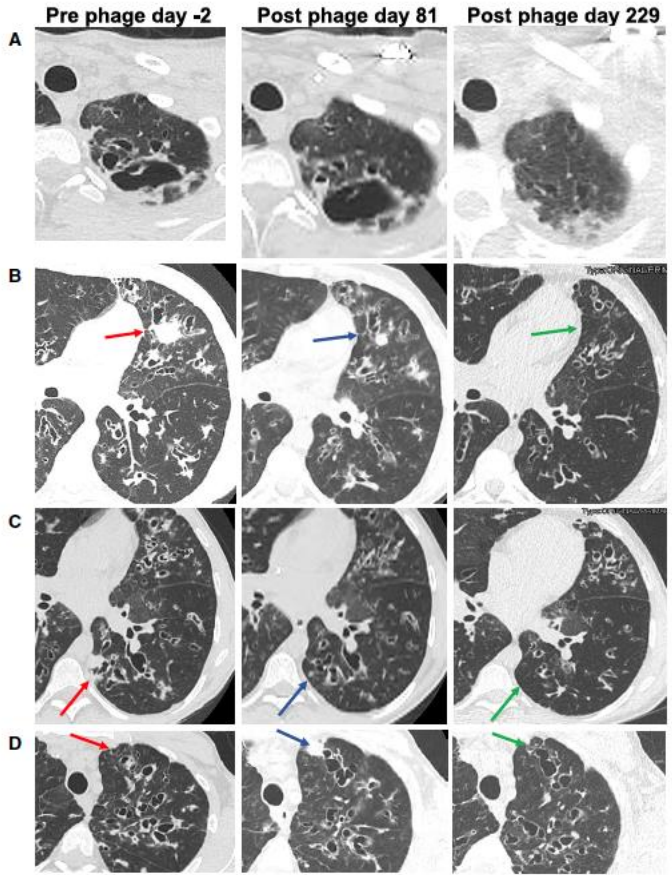
- 26 year old man with cystic fibrosis
- Chronic MRSA and *Pseudomonas aeruginosa* infections
- Treated for MAC lung infection 5 years earlier
- *M. abscessus* subspecies *abscessus* isolated
- Treated with 4 to 5 drugs for over 4 years
- Remained culture positive with declining FEV1



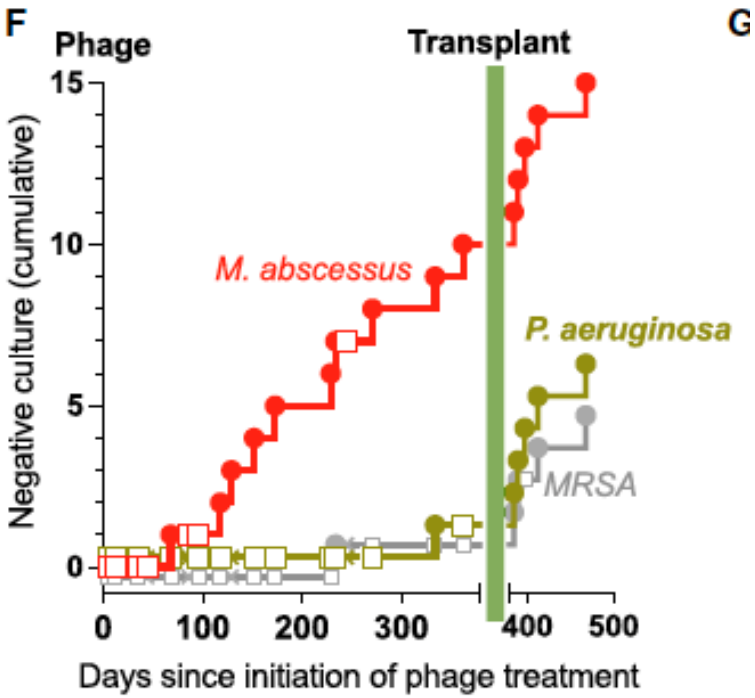
Nick J, et al. Cell 2022

Treatment Outcomes with Phage Therapy

Radiographic Improvement

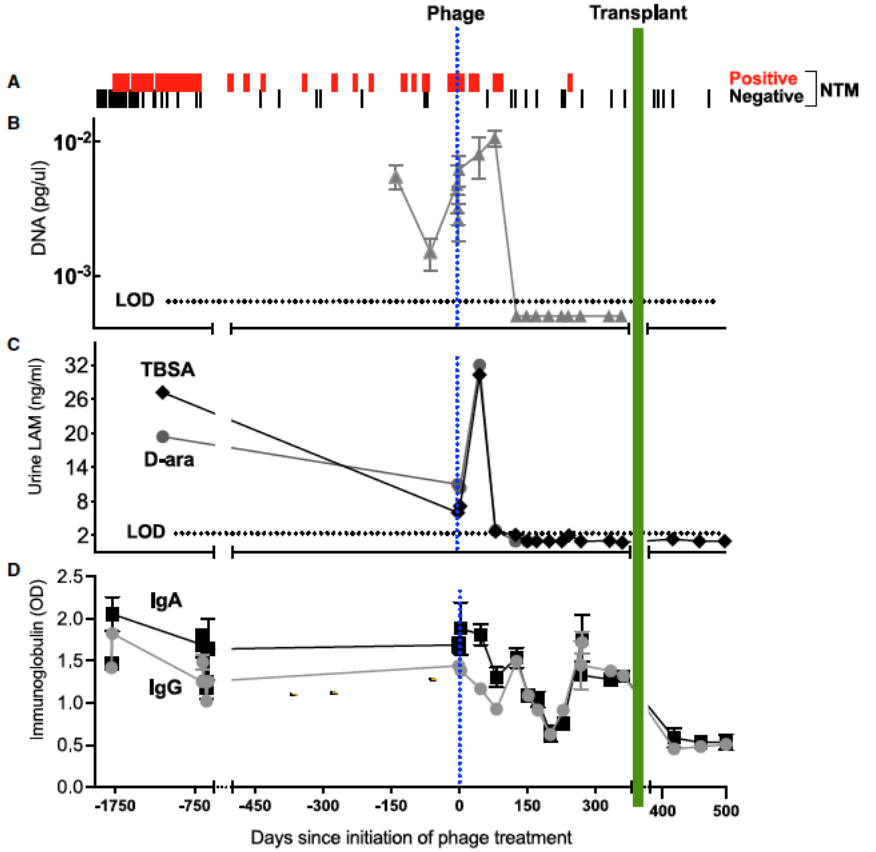


Culture Conversion



Nick J, et al. Cell 2022

Biomarker Changes



Phage Therapy for Mycobacterial Infections in 20 Persons

- Isolates from 200 patients were screened for phage susceptibilities
  - One or more lytic phages were identified for 55 isolates
- Phage were administered intravenously, through inhalation or both in 20 patients with symptomatic mycobacterial infections
- Results:
  - No adverse reactions occurred
  - Favorable clinical or microbiologic responses were seen in 11 patients
  - Neutralizing antibody was identified in 8 patients possibly contributing to lack of treatment response
  - A single phage was administered in 11 patients and no phage resistance was identified

Dedrick R, et al. CID 2022

Drug Development Pipeline for NTM Drugs: Phase 1-3

Phase 1	Phase 2	Phase 3
Gallium	Bedaquiline	Amikacin liposome
Apramycin	Clofazimine	inhalation suspension (ALIS)
	Epetraborole	RHB-204
	IL-7	Azithromycin vs clarithromycin
	Inhaled GM-CSF	Clarithromycin vs moxifloxacin
	Inhaled nitric oxide	2 vs 3 drugs for MAC
	Omadacycline	
	SPR720	

ClinicalTrials.gov