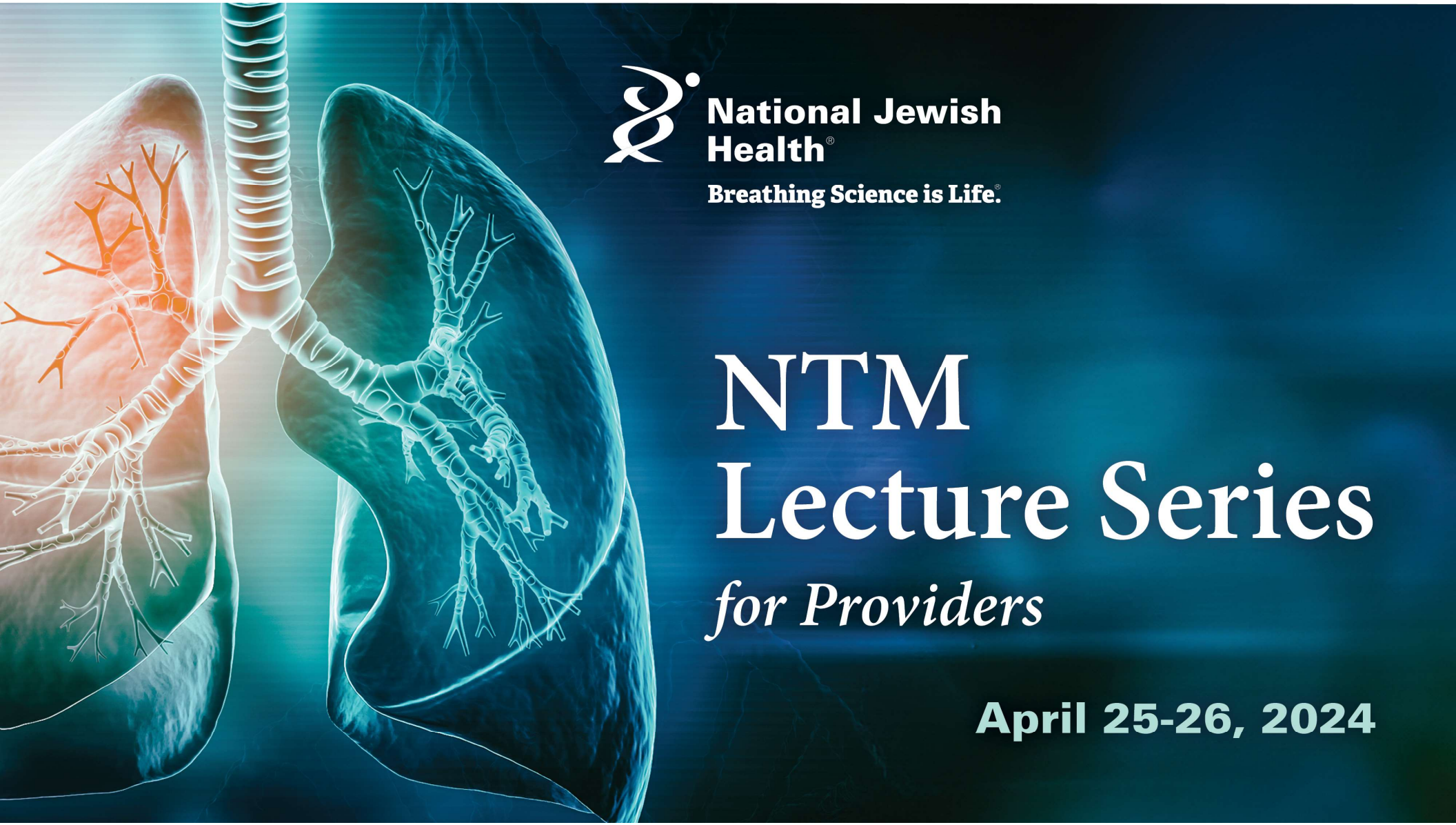

National Jewish Health®
Breathing Science is Life®
NTM
Lecture Series
for Providers
April 25-26, 2024

Novel Therapies for NTM Infections

Charles L. Daley, MD
Professor of Medicine
National Jewish Health,
University of Colorado,
Icahn School of Medicine, Mt. Sinai

Chief, Division of Mycobacterial and Respiratory Infections
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

National Jewish Health

Clinical Pipeline for NTM Drugs

Gallium
Apramycin

Bedaquiline
Clofazimine
Epetraborole
IL-7
Inhaled GM-CSF
Inhaled nitric oxide
Omadacycline
SPR720

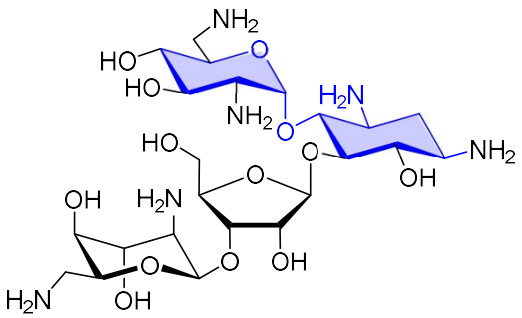
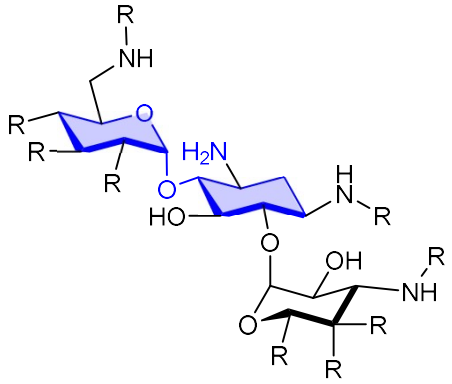
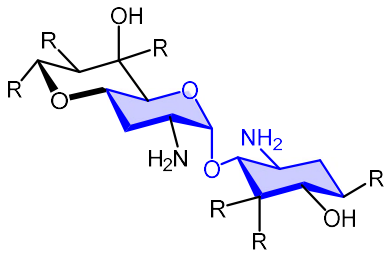
Amikacin liposome inhalation suspension (ALIS)
Azithromycin vs clarithromycin
Clarithromycin vs moxifloxacin
2 vs 3 drugs for MAC

Green – recruiting
Blue – not yet recruiting
Red – completed
Black – on hold

National Jewish Health
Science Transforming Life

National Jewish Health
ClinicalTrials.gov

Apramycin – an aminoglycoside

neomycin	kanamycins	apramycins
		
Neomycin	Amikacin, plazomicin, kanamycin, gentamicin, tobramycin, netilmicin	Apramycin
(4,5-disubstituted deoxystreptamine)	(4,6-disubstituted deoxystreptamines)	(octadiose-substituted deoxystreptamines)
Most toxic	**Less toxic**	**Least toxic**

Source: Juvabis

National Jewish Health

Apramycin

- New aminoglycoside subclass
- Less toxic than comparator aminoglycosides
  - (PNAS 109(27):10984; Sci Rep 9(1):2410; EBioMed 73:103652)
- Evades almost all aminoglycoside resistances
  - (PNAS 109(27):10984; JAC 74(4):944)
- High lung penetration following parenteral administration
  - (CMI 27(9):1315; NCT05590728)
- Potent in-vivo efficacy in CF mice, both subcutaneous & inhaled
  - (AAC 66(2):e0151021; manuscripts in prep.)

Source: Juvabis

National Jewish Health

Apramycin MIC Distribution for Select NTM

828 NTM Isolates

- 427 RGM
- 401 SGM

APR and AMK MICs by broth microdilution (CLSI, M24, 2018)

Data Analysis and Statistical Summary

- MIC distributions
- MIC_{50} , MIC_{90}
- TECOFFs

Study Laboratories:

- National Jewish Health
- University of Zurich
- Research Institute of TB, Japan

National Jewish Health

Nguyen MV, et al. 2024 ESCMID

Apramycin MIC Distribution for Rapidly Growing NTM

Target	Drug	*n*	MIC (mg/L)			MIC_{50}	MIC_{90}
			Lowest	Modal	Highest		
MAB	APR	358	0.5	2	>128	2	4
	AMK	358	0.5	16	>128	16	32
M. chelonae	APR	25	2	2	>128	2	4
	AMK	25	8	8	>128	16	16
M. fortuitum	APR	44	0.5	1	4	1	4
	AMK	44	0.5	1	4	1	2

Nguyen MV, et al. 2024 ESCMID

National Jewish Health

Apramycin MIC Distribution for Slowly Growing NTM

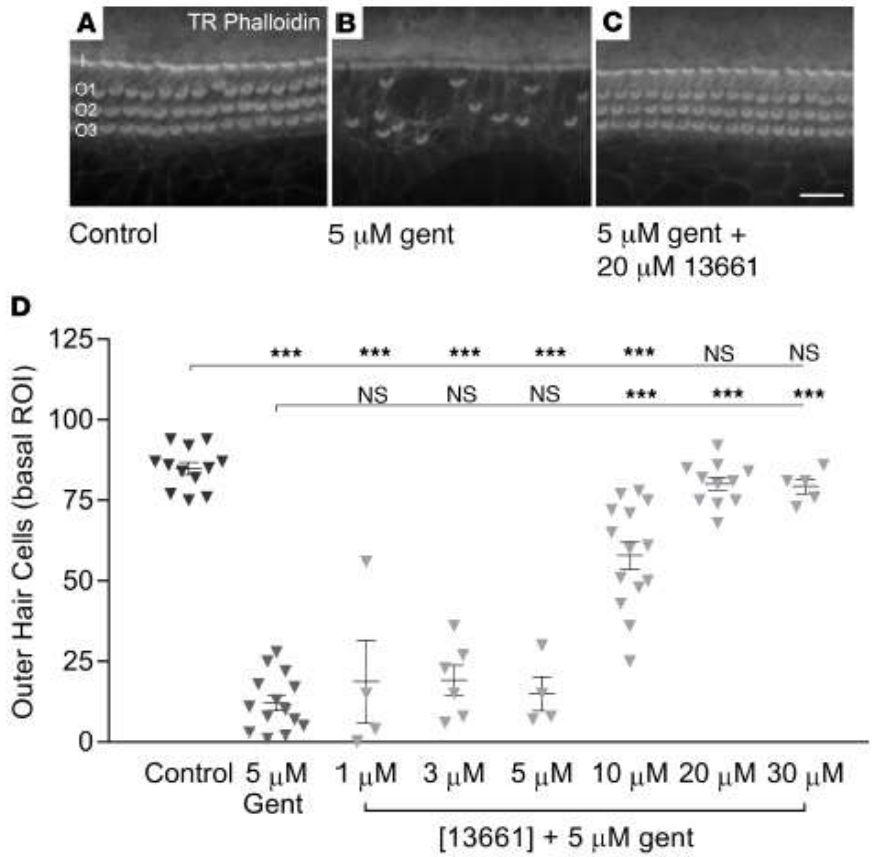
Target	Drug	*n*	MIC (mg/L)				
			Lowest	Modal	Highest	MIC_{50}	MIC_{90}
MAC	APR	360	0.25	16	>128	16	32
	AMK	360	0.25	16	>128	16	32
M. kansasii	APR	31	0.25	2	16	2	8
	AMK	31	0.5	2	16	2	8

National Jewish Health

Nguyen MV, et al. 2024 ESCMID

ORC-13661- Protects mouse sensory hair cells from aminoglycoside ototoxicity

- Aminoglycosides damage the sensory hair cells in the cochlea and vestibular end organs of the inner ear
- In the cochlea, the outer hair cells are more susceptible than the inner hair cells
- Aminoglycoside entry into the hair cells is predominantly via the mechanoelectrical transducer (MET) channels
- ORC-13661 is thought to be a competitive blocker of the MET channel preventing entry of aminoglycosides into the hair cell



Kitcher SR, et al. JCI Insight 2019;4:e126764

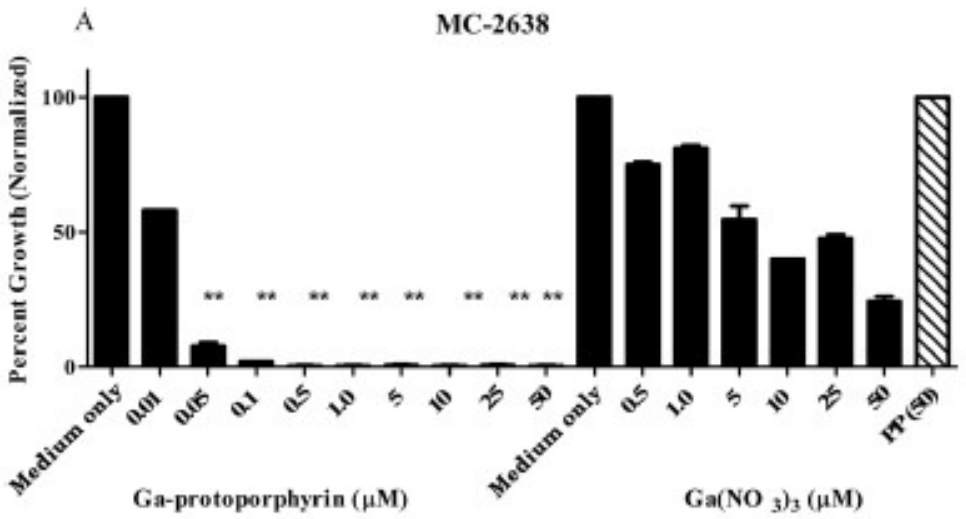
Gallium

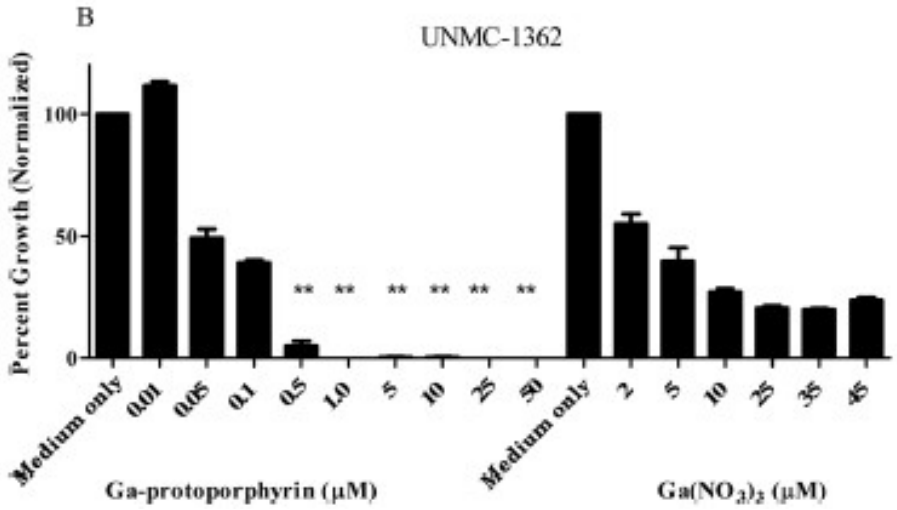
- Iron is essential for the growth of mycobacteria
  - Iron is important in DNA synthesis, metabolism, and oxidative stress responses
- Control of availability or interference with Fe update inhibits growth of *M. tuberculosis* and virulence is increased with greater availability
- Gallium can compete with Fe and inhibit Fe-dependent enzymes in mycobacteria
- Ga $(NO_3)_3$ [gallium nitrate) is FDA approved for hypercalcemia of malignancy

National Jewish Health

Abdalla MY, et al. AAC 2015;59:4826-34

Gallium: Inhibition of *M. abscessus*





* P <0.001

National Jewish Health

Abdalla MY, et al. AAC 2015;59:4826-34

A Phase 1b, Multi-center Study of Intravenous (IV) Gallium Nitrate in Patients With Cystic Fibrosis (CF) Who Are Colonized With Nontuberculous Mycobacteria (NTM) (The ABATE Study)

- The purpose of this study is to assess the safety and tolerability of IV gallium in adults with CF who are infected with NTM
- This is a prospective, multicenter open-label study in adults with CF who are “colonized” with *M. avium* complex and/or *M. abscessus*
- Gallium nitrate will be infused continuously over 5 days at 200 mg/m2/day. There is a maximum of 2 cycles.
- Primary outcome: Proportion of patients experiencing one or more Adverse Events of Special Interest (AESI). AESIs include:
  - the occurrence of either (1) a serious adverse event (SAE) of grade 3 or higher including hospitalizations or (2) study drug discontinuation because of an AE.
- Secondary outcome: Proportion of subjects who were NTM culture positive at baseline and have at least 2 sequential negative NTM cultures between visits 2 (Day 6) and 7 (Day 111). Those negative cultures must be at least 2 weeks apart.

ClinTrial.gov

National Jewish Health

Epetraborole – in vitro activity against MAC

- Epetraborole inhibits the protein synthesis enzyme leucyl-tRNA synthetase by binding to the terminal adenosine ribose of tRNA

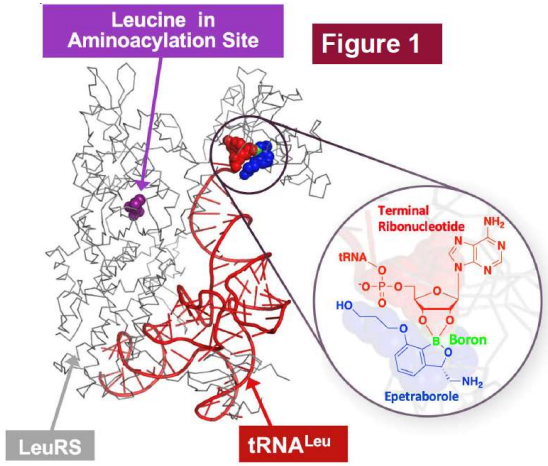


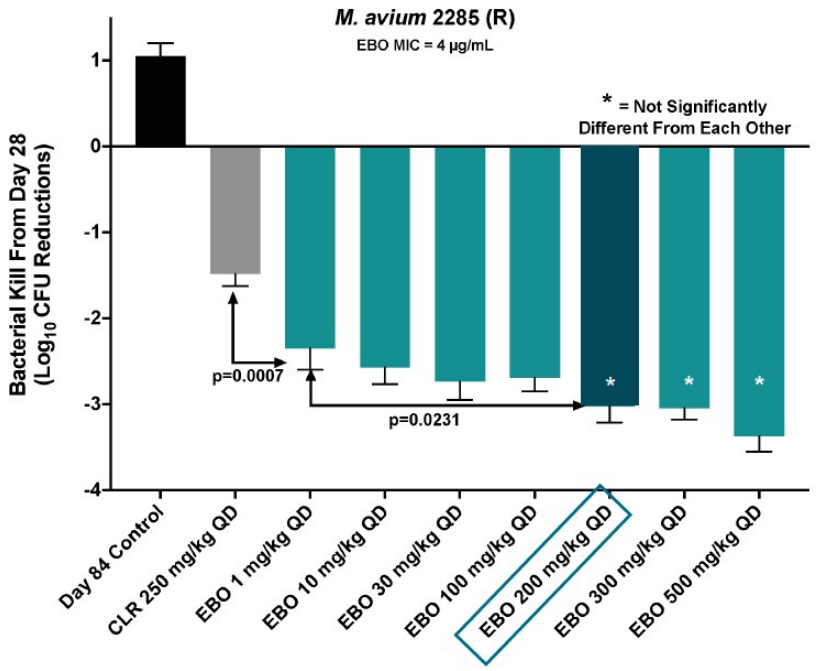
Table 3. In Vitro Activity Against 51 Isolates of MAC

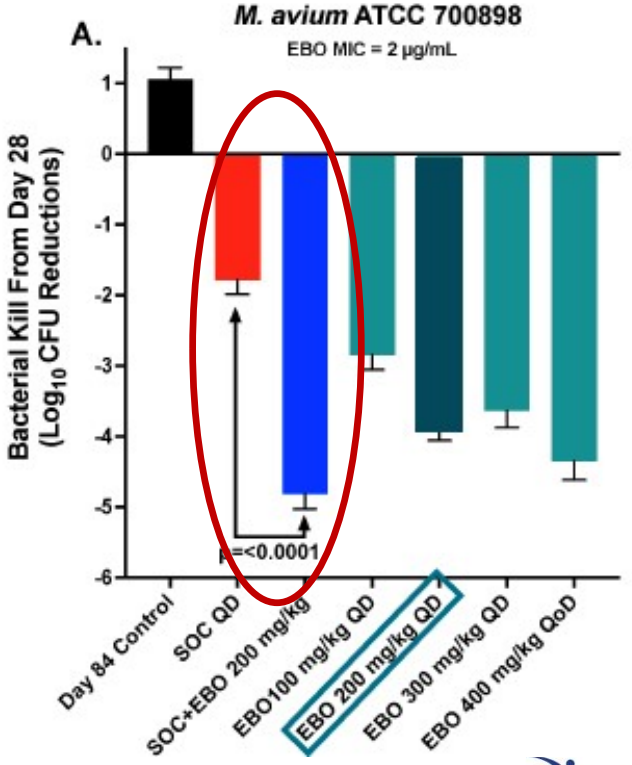
Compound	MIC Parameter (mg/L)	CAMHB + 5% OADC	7H9 + 5% OADC
Epetraborole (EBO)	MIC Range	0.25-8	0.25-8
	MIC Modal	2	1
	MIC_{50}	2	1
	MIC_{90}	8	4
Clarithromycin (CLR)	MIC Range	0.25->64	0.25->64
	MIC Modal	1	4
	MIC_{50}	1	2
	MIC_{90}	4	8
Amikacin (AMK)	MIC Range	8->64	8-32
	MIC Modal	64	16
	MIC_{50}	16	16
	MIC_{90}	64	16

National Jewish Health

DeStefano MS, et al. Poster 1712, ID Week, Oct 2022

Epetraborole – activity against MAC in a chronic mouse model



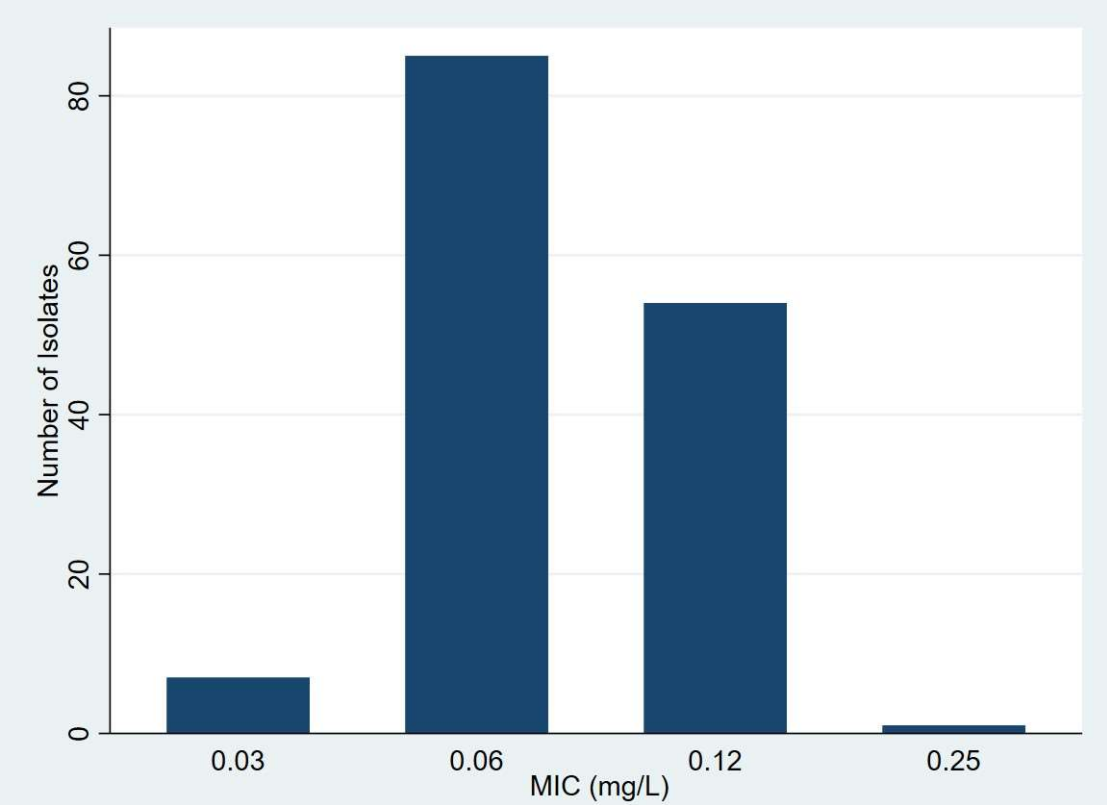


National Jewish Health

De K, et al. Poster 1704. ID Week. October 2022

Distribution of Epetraborole Minimal Inhibitory Concentrations Against *Mycobacterium abscessus*

- 147 MAB isolates
  - 122 from respiratory sources in the US, collected in 2021
  - 25 from respiratory and other sources in Europe, collected in 2019-2022
- Susceptibility done by broth microdilution according to CLSI guidance using frozen microtiter panels manufactured by ThermoFisher against EBO and a panel of 13 antimicrobials with anti-MAB activity
- MIC values were determined after 4-5 days of incubation



National Jewish Health

Nguyen, V, et al. IDWeek 2023, Boston, MA, USA, October 14th, 2023

Distribution of Epetraborole Minimal Inhibitory Concentrations Against *Mycobacterium abscessus*

	Number (%) of isolates inhibited at specific MIC (mg/L)			
	0.03	0.06	0.12	0.25
All (n = 147)	7 (4.8)	85 (57.8)	54 (36.7)	1 (0.7)
Subspecies				
abscessus (n = 101)	3 (3)	58 (57.4)	39 (38.6)	1 (1)
bolletii (n = 6)	0 (0)	5 (83.3)	1 (16.7)	0 (0)
massiliense (n = 40)	4 (10)	22 (55)	14 (35)	0 (0)

MIC, minimal inhibitory concentration.

MIC_{50} MIC_{90}

Nguyen, V, et al. IDWeek 2023, Boston, MA, USA, October 14th, 2023

National Jewish Health

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
  - 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

National Jewish Health

In vitro Activity of Omadacycline, Tigecycline, and Eravacycline Against *M. abscessus* subspecies

			Omadacycline	
Study	No. Isolates	Subpecies	MIC_{50}	MIC_{90}
Shoen, et al	24	*M. abscessus*	1	2
Kaushik, et al	16 12	*M. abscessus* *M. massiliense*	2 1	4 2
Brown-Elliott, et al	20 3	*M. abscessus* *M. massiliense*	0.12 0.12	0.25
Nicklas, et al	12 9	*M. abscessus* *M. massiliense*	0.25 0.375	0.5 1
Zhang, et al	44 29	*M. abscessus* *M. massiliense*	0.5 1	1 2
Li, et al	147 46	*M. abscessus* *M. massiliense*	1 2	4 4

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
Nicklas DA, et al. Antimicrob Agents Chemother 63e0170421
Zhang T, et al. Microbiol Spectr 11:e0323822
Li, et al. Microbiol Spectr 10.e00718

National Jewish Health

In vitro Activity of Omadacycline, Tigecycline, and Eravacycline Against *M. abscessus* subspecies

			Omadacycline		Tigecycline	
Study	No. Isolates	Subpecies	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Shoen, et al	24	*M. abscessus*	1	2	1	2
Kaushik, et al	16 12	*M. abscessus* *M. massiliense*	2 1	4 2	1 1	2 2
Brown-Elliott, et al	20 3	*M. abscessus* *M. massiliense*	0.12 0.12	0.25	0.12 0.25	0.25
Nicklas, et al	12 9	*M. abscessus* *M. massiliense*	0.25 0.375	0.5 1	0.19	0.25 0.5
Zhang, et al	44 29	*M. abscessus* *M. massiliense*	0.5 1	1 2	0.5 0.5	1 1
Li, et al	147 46	*M. abscessus* *M. massiliense*	1 2	4 4	0.5 1	2 2

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
Nicklas DA, et al. Antimicrob Agents Chemother 63e0170421
Zhang T, et al. Microbiol Spectr 11:e0323822
Li, et al. Microbiol Spectr 10.e00718

National Jewish Health

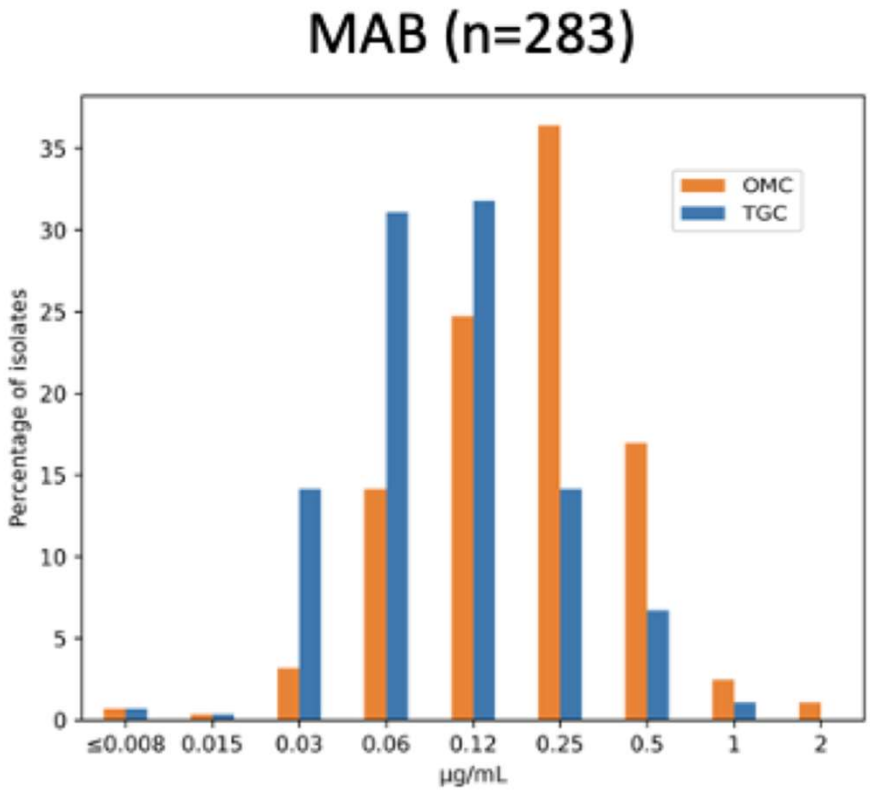
In vitro Activity of Omadacycline, Tigecycline, and Eravacycline Against *M. abscessus* subspecies

			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 12	*M. abscessus* *M. massiliense*	2 1	4 2	1 1	2 2	0.5	1
Brown-Elliott, et al	20 3	*M. abscessus* *M. massiliense*	0.12 0.12	0.25	0.12 0.25	0.25	-	-
Nicklas, et al	12 9	*M. abscessus* *M. massiliense*	0.25 0.375	0.5 1	0.19	0.25 0.5	-	-
Zhang, et al	44 29	*M. abscessus* *M. massiliense*	0.5 1	1 2	0.5 0.5	1 1	0.12 0.12	0.25 0.25
Li, et al	147 46	*M. abscessus* *M. massiliense*	1 2	4 4	0.5 1	2 2	1 1	4 4

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
Nicklas DA, et al. Antimicrob Agents Chemother 63e0170421
Zhang T, et al. Microbiol Spectr 11:e0323822
Li, et al. Microbiol Spectr 10.e00718

National Jewish Health

Omadacycline and Tigecycline MIC (µg/mL) Distributions for *M. abscessus* isolates"



Species	n	OMC MIC (µg/mL)			TGC MIC (µg/mL)		
		MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
M. abscessus	283	0.25	0.5	≤0.008 - 2	0.12	0.25	≤0.008 - 1
M. chelonae	13	0.25	0.5	0.06 - 0.5	0.12	0.25	0.015 - 0.5
M. fortuitum	16	0.25	0.5	0.06 - 0.5	0.06	0.12	≤0.008 - 0.12

National Jewish Health

Calado Nogeira de Moura V, et al. 2024. ESCMID

Omadacycline Case Series

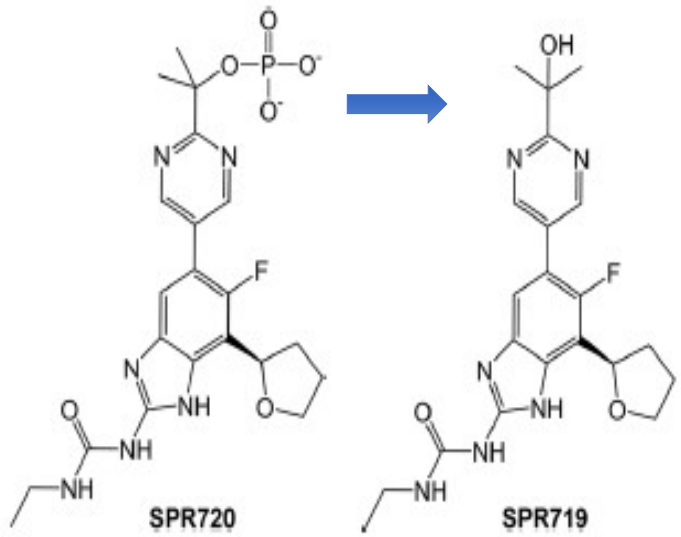
Study (date)	N	Site of Infection	AEs Due to Omadacycline	Outcome
Pearson (2020)	4	Pulmonary (1) Extrapulmonary (3)	N/V (1)	75% Cured
Morrisette (2021)	12	Pulmonary (7) Extrapulmonary (5)	GI (1) Increased Cr (1) Increased AST/ALT	75% clinical success
Duah (2022)	3	Pulmonary (3)	N/V (1)	100% clinical success 2/3 culture negative
Siddiqa (2023)	5	Pulmonary (1) Extrapulmonary (4)	?	100% clinical success 4 SSTI completed treatment
Mingora (2023)	117	Pulmonary 80% Extrapulmonary 20%	29.9% had AE 22% discontinued N/V in 21%	17 (18%) culture converted 27 (29%) had negative culture at final assessment

Pearson JC, et al. OFID 2020;7:ofaa415
Duah M, et al. In J Infect Dis 2022;122:953-956
Morrisette T, et al. OFID 2021;8:ofab002
Siddiqu A, et al. IDCases 2023;31:e01703
Mingora C, et al, OFID 2023;10:ofad335

National Jewish Health

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



National Jewish Health

Aragaw WW, et al. Micro Spectrum 2022;10:e01321-21

In vitro Activity of SPR719

NTM species	N[1]	MIC range	MIC50	MIC90	N[2]	MIC range	MIC50	MIC90
MAC	73	0.06-4	1	2	31	0.12-2.0	0.5	2
M. kansasii	21	<0.03-0.25	<0.03	0.125	8	0.002-0.03	0.015	0.03
M. simiae	4	2-8	NA	NA	10	0.5-4.0	1	2
M. malmoense	3	0.06-0.5	NA	NA	–	–	–	–
M. xenopi	5	0.06-0.5	NA	NA	–	–	–	–
M. abscessus	32	1->32	2	8	33	0.25-8.0	2	4
M. massiliense	–	–	–	–	10	0.12-4.0	2	2

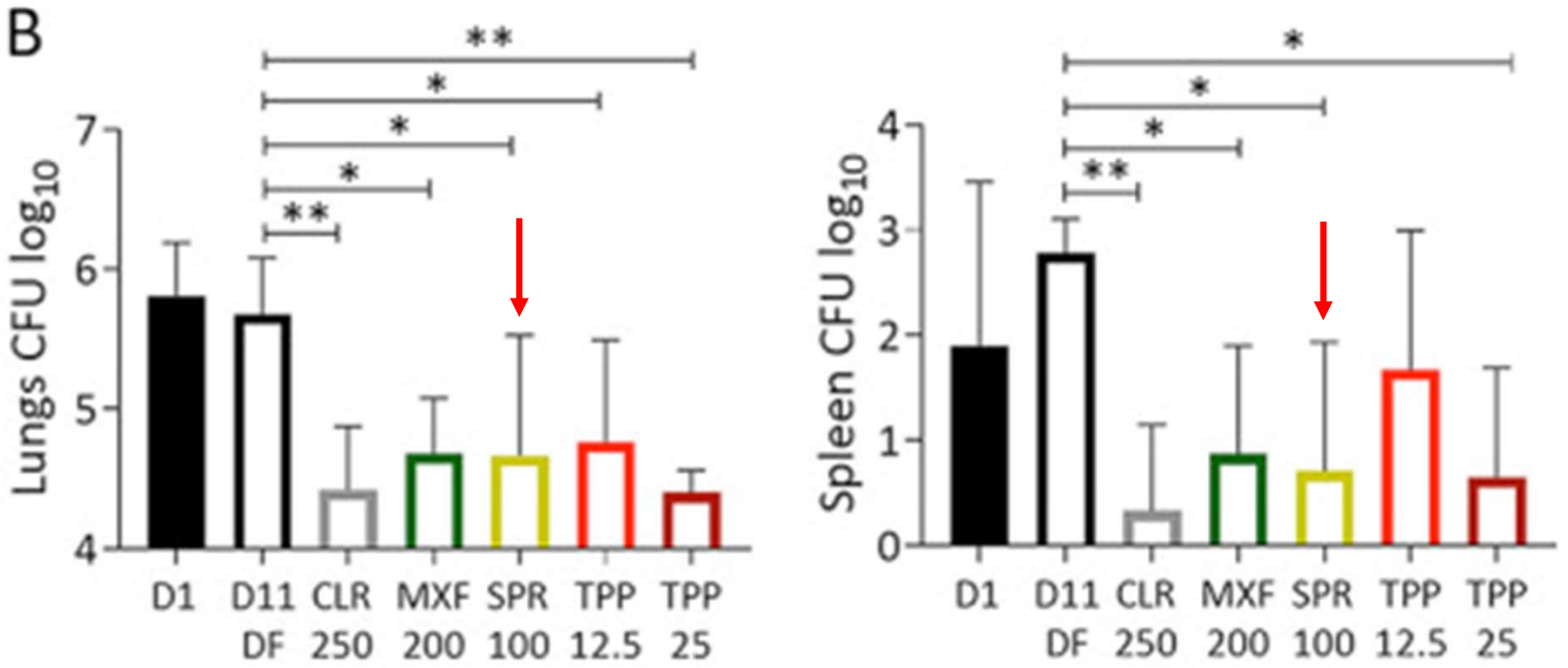
MAC- *M. avium* complex; NA – not applicable

- Bactericidal activity against *M. kansasii*

1. Pennings LJ, et al. Antimicrob Agents Chemother 2021;65:e02469-02
2. Brown-Elliot BA, et al. Antimicrob Agents Chemother 2018;62:e01503-18

National Jewish Health

Activity of Tricyclic Pyrrolopyrimidine Gyrase B Inhibitor and SPR720 Against *M. abscessus* in Murine Model



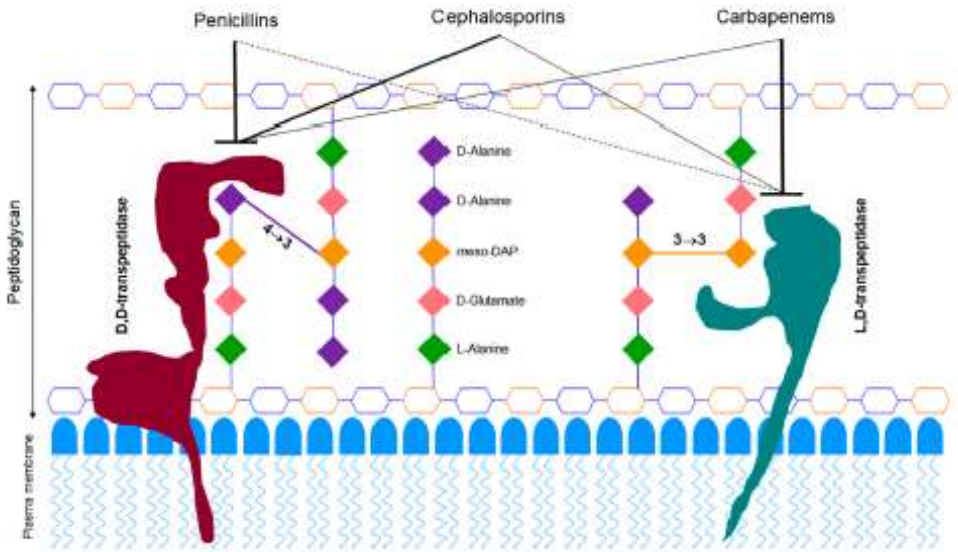
Madani A, et al. Antimicrob Agents Chemother 2022;66:1-7

National Jewish Health

Mycobacterium abscessus: β-lactamases

- *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

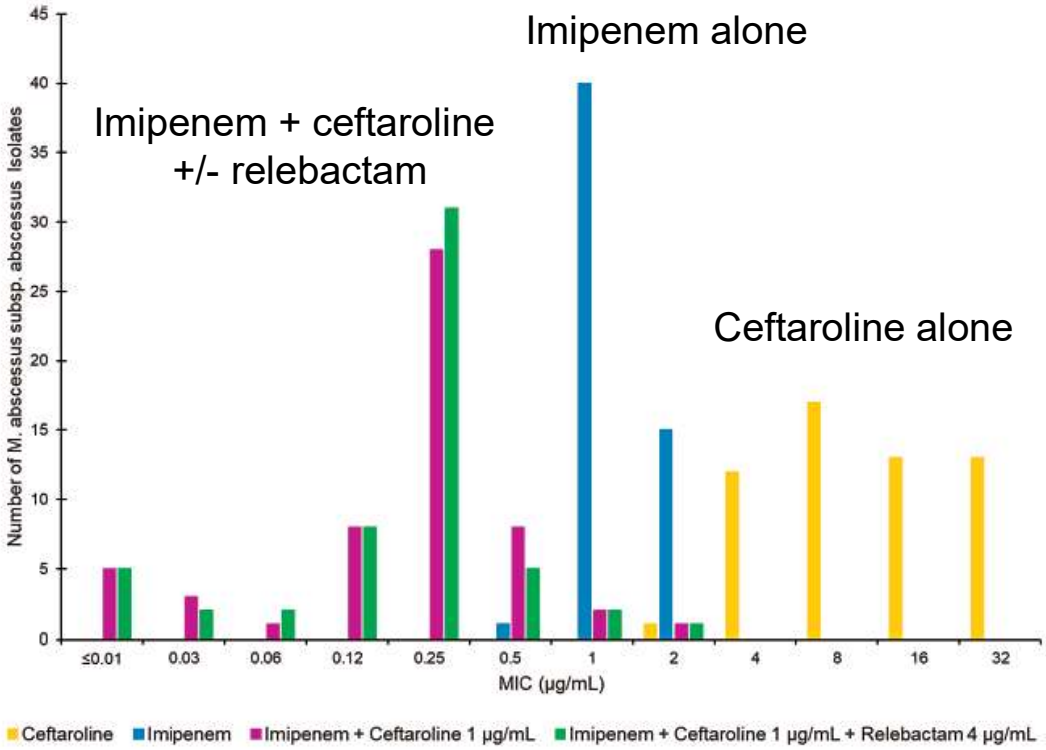
Model of *M. abscessus* Peptidoglycan



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

National Jewish Health

In vitro Activity Imipenem, Ceftaroline and Combination



- Imipenem and ceftaroline bind the same targets including multiple L,D-transpeptidases and D,D carboxypeptidase 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

National Jewish Health

79 year old woman with remote history of pulmonary TB with right upper lobe ant. and post. segmentectomies. Now with *M. abscessus*

5/19 – started on treatment
- Amikacin (IV) 500 mg MWF
- Imipenem (IV) 500 mg twice daily
- Clofazimine 100 mg daily

7/19 – changed to inhaled amikacin and clofazimine
10/19 – restarted on treatment

12/19 - Ceftaroline 600 mg twice daily was added to the regimen

6/20 - Gained 5 kg, normalized CRP and albumin and converted cultures to negative. Has remained negative for ~ 4 years

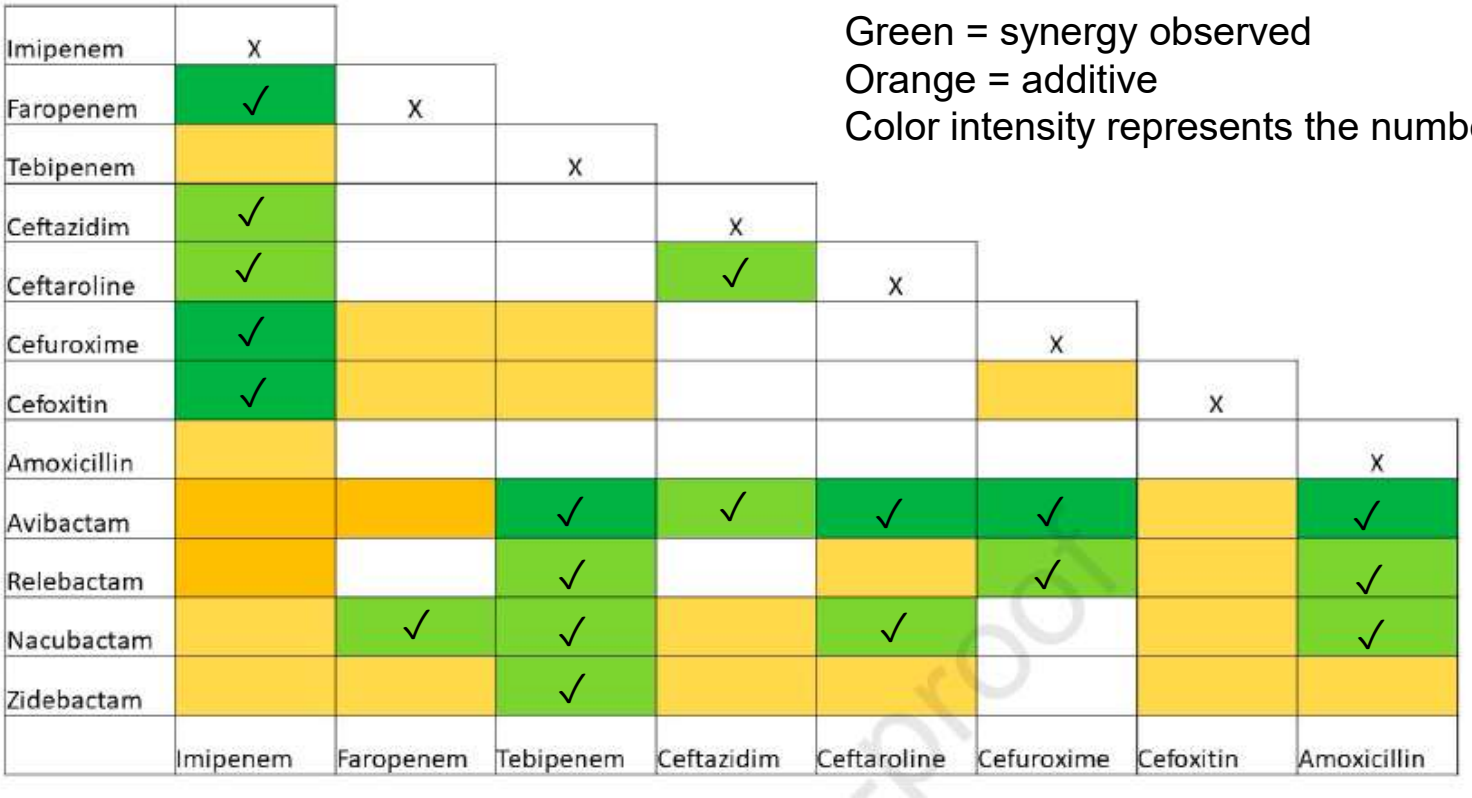
5/19

12/19

6/20

National Jewish Health

Summary of In Vitro Synergy Between β-lactams and β-lactamase Inhibitors

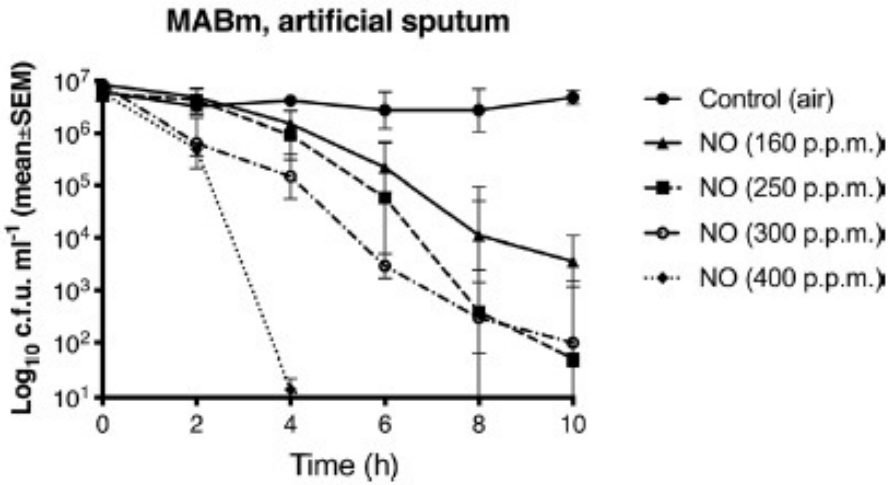


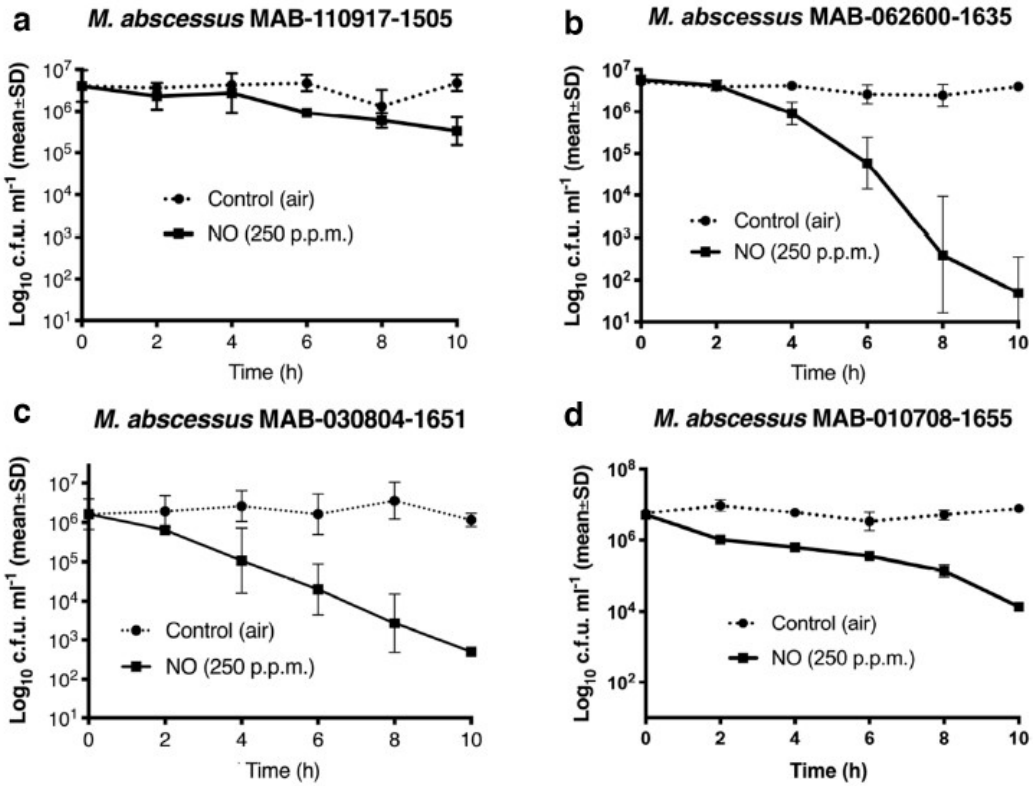
Green = synergy observed
Orange = additive
Color intensity represents the number of studies

Torres MP, et al. Clin Micro Infect 2024;https://doi.og/10.1016/j.cmi.2024.03.019

National Jewish Health

Inhaled Nitric Oxide Activity Against *M. abscessus*



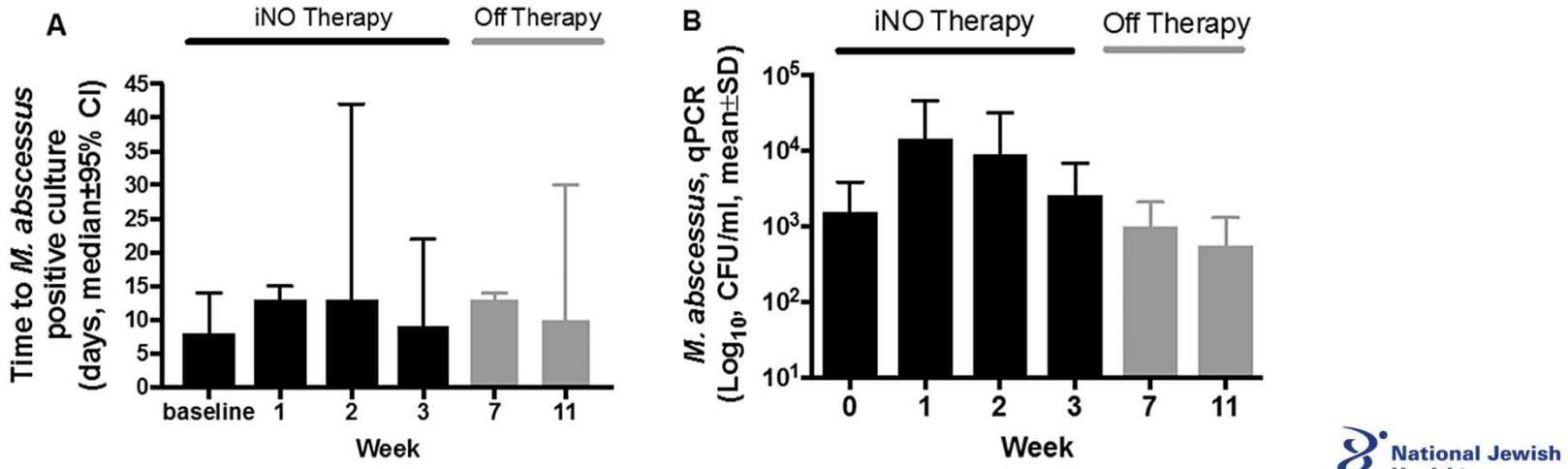


National Jewish Health

Bogdanovski K, et al. Access Micro 2020:2

Inhaled Nitric Oxide

- Prospective, open-label pilot study of iNO (160 ppm) administered 5 times/day for 14 days then 3 times/day for 7 days
- 9 subjects with *M. abscessus* pulmonary disease were enrolled
  - No SAEs reported
  - Mean FEV1 and 6MWD increased during iNO treatment (not significant)
  - Culture conversion was not achieved
  - Mean time to positivity and qPCR analysis showed reductions in sputum bacterial load



Bentur L, et al. J Cystic Fibrosis 2020;19:225-231

National Jewish Health

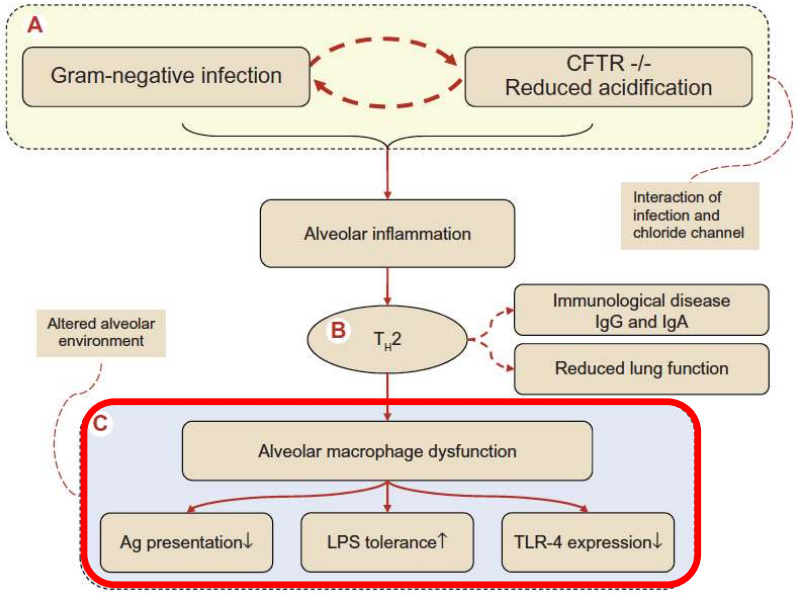
Inhaled NO in Adults with NTM Pulmonary Disease

- Patients with NTM lung disease who had persistently positive cultures
  - 10 patients (9 were on long term antimicrobial therapy)
- Treated with nitric oxide gas (gNO) for 50 minutes three times daily, five days a week for three weeks (total-15 treatment days)
- Results:
  - 4 (40%) patients had negative cultures after 3 weeks of therapy
  - Following treatment cessation, 3 became culture positive again
  - Treatment was well tolerated with no discontinuations

Flume P, et al. Resp Med 2023;206:107069

National Jewish Health

Alveolar Macrophage Dysfunction in Cystic Fibrosis



Heslet L, et al. J Inflamm Res2012;5:19-27

- Alveolar Macs from GM-CSF -/- mice exhibit:
  - defective phagocytosis,
  - bacterial killing, and
  - reduced H_2O_2 production
- GM-CSF knockout models of *M. abscessus* infection are more susceptible than wild-type mice

Ballinger MN, et al. AJRCMB 2006;34:766
De Groote MA, et al. J Antimicrob Chemother 2014;69:1057

National Jewish Health

Inhaled GM-CSF in Treatment Refractory NTM

- 32 patients with chronic, culture positive NTM (24 MAC, 8 MAB)
  - 16 on guideline-based therapy
  - 16 not on guideline-based therapy
- Inhaled GM-CSF (molgramostim) 300 µg/day over 48 weeks
- Results:
  - 8 patients (25%) achieved culture conversion (durable in 4)
    - 7 with MAC, 1 with MAB
  - Among 24 with MAC, additional 4 converted smears to negative
  - Clinical endpoints did not improve
  - SAEs were generally due to pulmonary exacerbations or worsening NTM infection

Thomson RM, et al. Ann Am Thorac Soc 2024:21:568-576

National Jewish Health

Inhaled GM-CSF in Treatment Refractory NTM in People with Cystic Fibrosis

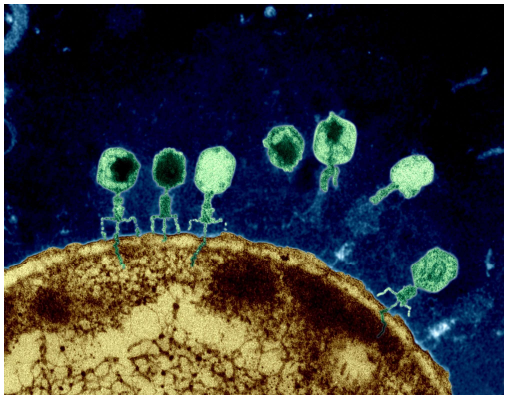
- 14 people with CF enrolled (28 screened)
  - Group 1 - 7 on guideline-based therapy for at least 9 months and still culture positive
  - Group 2 - 3 not on guideline-based therapy and still culture positive for at least 28 days
  - Group 3 - culture positive but did not meet ATS criteria for disease
- Inhaled GM-CSF 300 µg/day over 48 weeks
- Results:
  - 7 patients (50.0%) achieved culture conversion (durable in 3)
  - Conversion varied among the 3 cohorts: Group 1 (43%) , Group 2 (33%), Group 3 (75%)
  - SAEs in 25%-33% and were generally due to pulmonary exacerbations

Nick J. unpublished data

National Jewish Health

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



Antimicrobial Agents and Chemotherapy

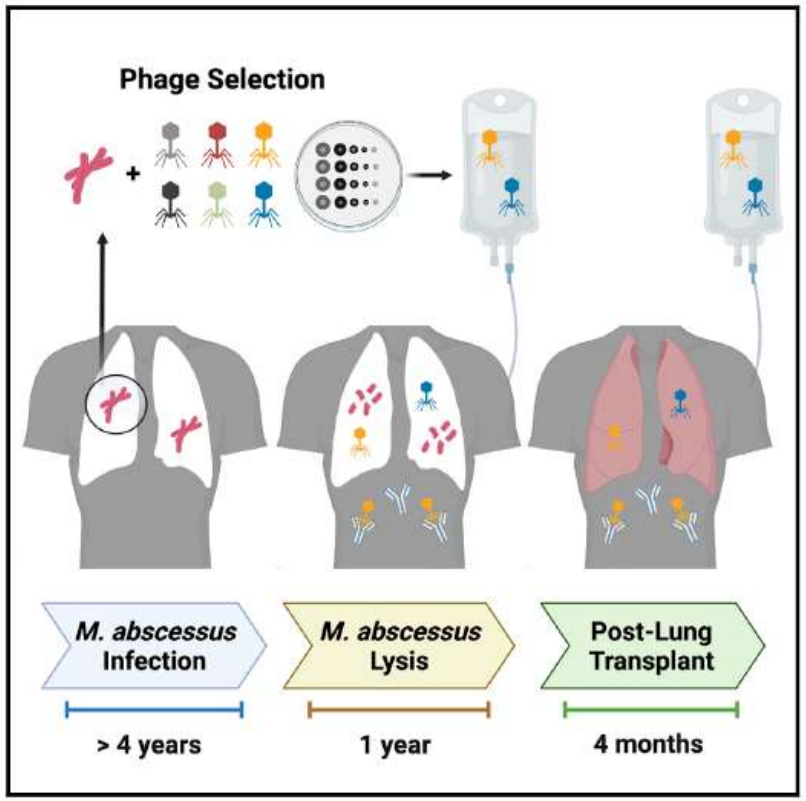
Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

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. Pico[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]

ıtional Jewish Health

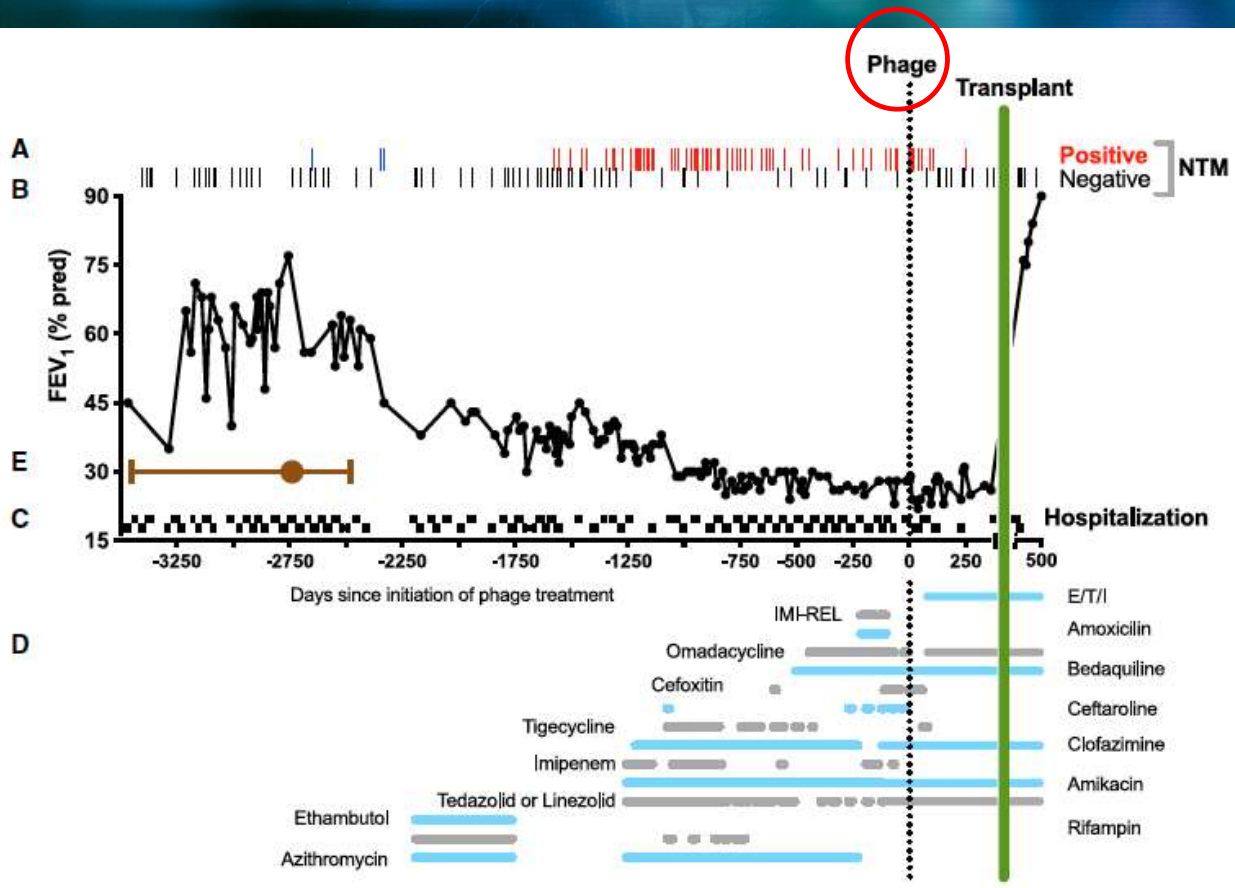
Mycobacteriophage Therapy for *M. abscessus*

- 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



National Jewish Health

Phage Therapy for *M. abscessus*

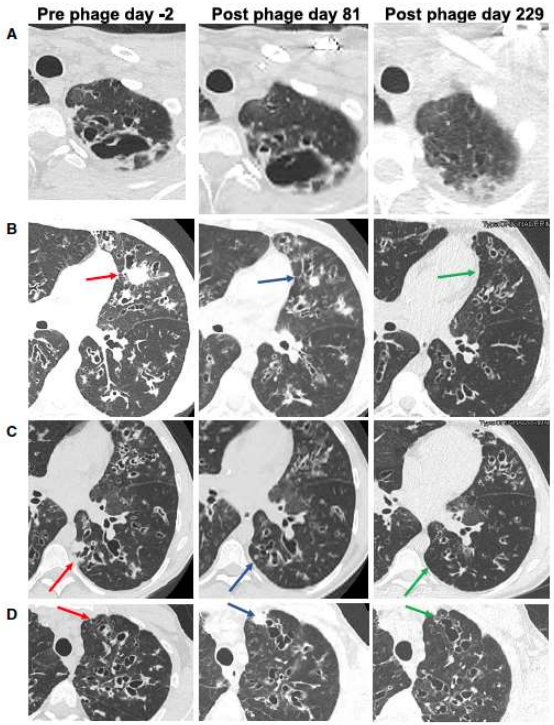


Nick J, et al. Cell 2022

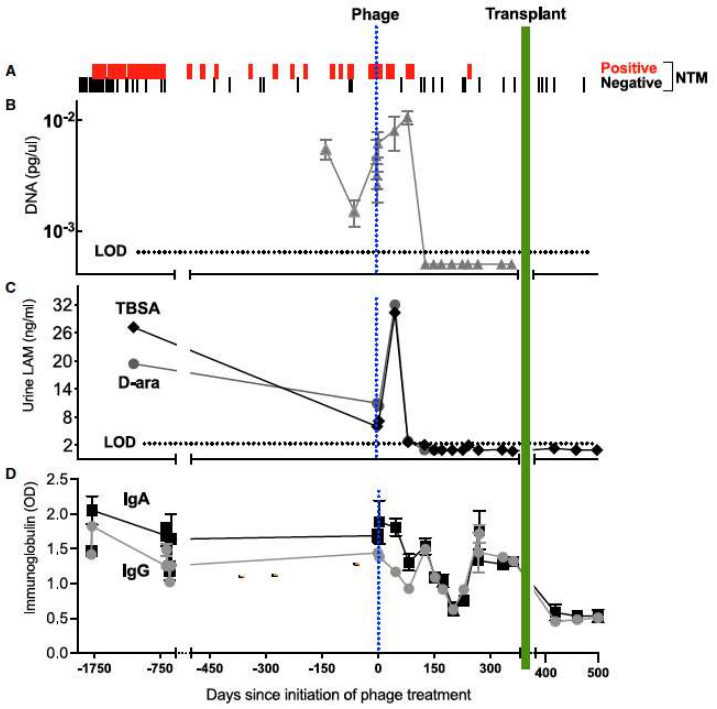
National Jewish Health

Treatment Outcomes with Phage

Radiographic Improvement



Biomarker Changes



National Jewish Health

Nick J, et al. Cell 2022

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

National Jewish Health

Phase 1 to 3 Clinical Trials in the US

Amikacin Liposome Inhalation Suspension - Study to Evaluate ALIS (Amikacin Liposome Inhalation Suspension) in Participants With Nontuberculous Mycobacterial Lung Infection Caused by ***Mycobacterium avium*** **Complex** (ENCORE)

Epetraborole - A Phase 2/3, Randomized, Double-blind, Placebo-controlled, Multicenter, Prospective Study to Assess the Efficacy, Safety, and Pharmacokinetics of Orally Administered Epetraborole in Patients With Treatment-refractory ***Mycobacterium avium*** Complex Lung Disease (ON HOLD)

Omadacycline - A Ph. 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, & Tolerability of Oral Omadacycline in Adults With NTM Pulmonary Disease Caused by ***Mycobacterium abscessus*** Complex (Recruiting)

SPR720 - A Randomized, Double-Blinded, Placebo-Controlled, Multicenter, Phase 2, Dose-Ranging Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of SPR720 as Compared With Placebo for the Treatment of Patients With Mycobacterium Avium Complex (MAC) Pulmonary Disease (Recruiting)

Gallium - A Phase 1b, Multi-center Study of Intravenous (IV) Gallium Nitrate in Patients With Cystic Fibrosis (CF) Who Are Colonized With **Nontuberculous Mycobacteria** (NTM) (The ABATE Study) (Recruiting)

ORC-13661 - Phase 2 Study of the Efficacy and Safety of ORC-13661 for the Prevention of Drug-Induced Hearing Loss in Patients Receiving Intravenous Amikacin for Treatment of **Non-Tuberculous Mycobacterium Disease** (Not yet recruiting)

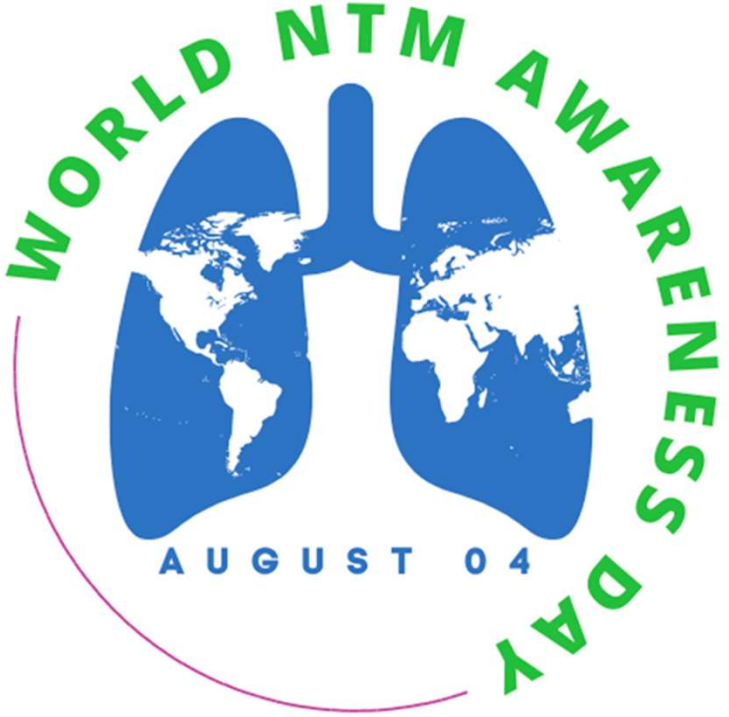
2 vs 3 Drugs - Comparison of Two- Versus Three-antibiotic Therapy for Pulmonary ***Mycobacterium avium*** **Complex** Disease (Recruiting)

Clofazimine - Phase 2 Study of Clofazimine for the Treatment of Pulmonary ***Mycobacterium avium*** complex Disease (Recruiting)

ClinicalTrials.gov

National Jewish Health

World NTM Awareness Day!



National Jewish Health