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)

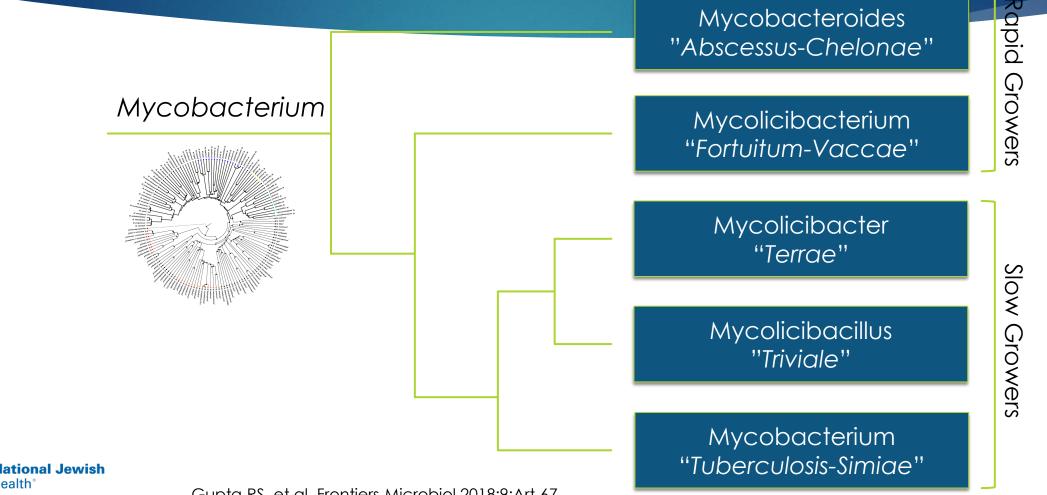
- Environmental bacteria
- Found in soil and water
- Produce both pulmonary and extrapulmonary disease
- Pathogenicity varies greatly
- High levels of in vitro resistance
- Treatment is complex and associated with suboptimal outcomes





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

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



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

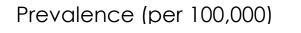
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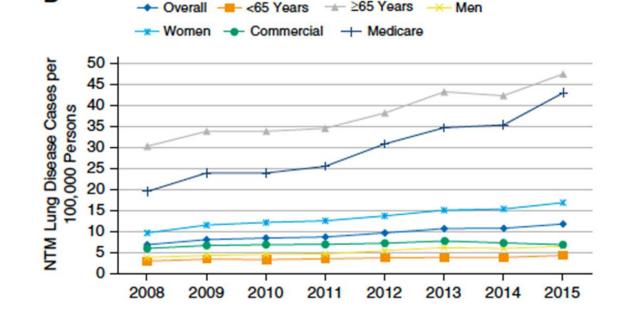
Nontuberculous Mycobacteria (NTM) High Prevalence of NTM-PD and Increasing

В

- 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

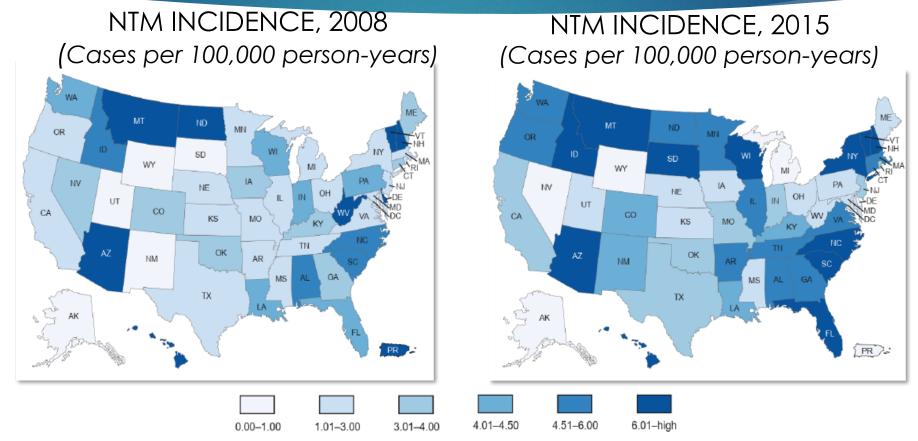






Winthrop KL, et al. Ann Am Thorac Soc. 2020;17(2):178-185.

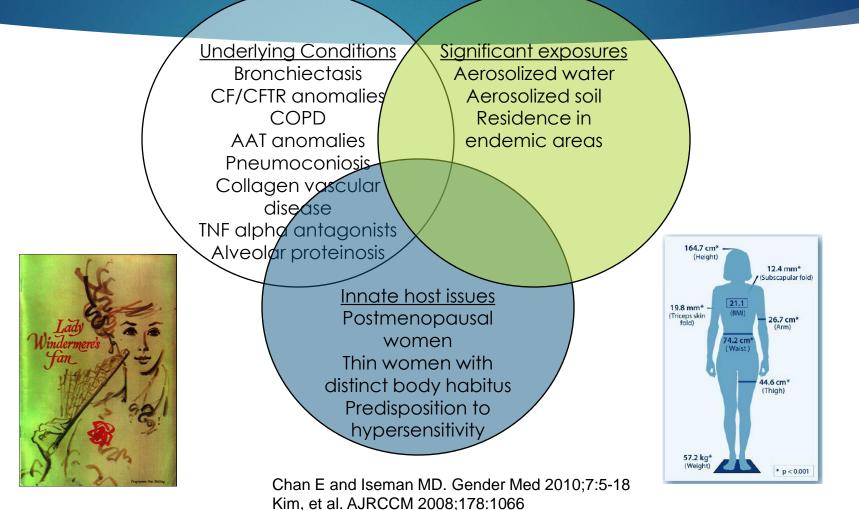
Increasing NTM US Incidence, 2008-2015





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

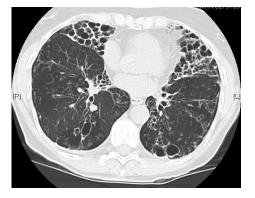
The Host - Risk Factors for NTM Infection

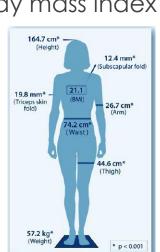


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Clinical Phenotypes

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





Fibrocavitary disease

- Male
- Older
- Smokers
- Various body builds



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



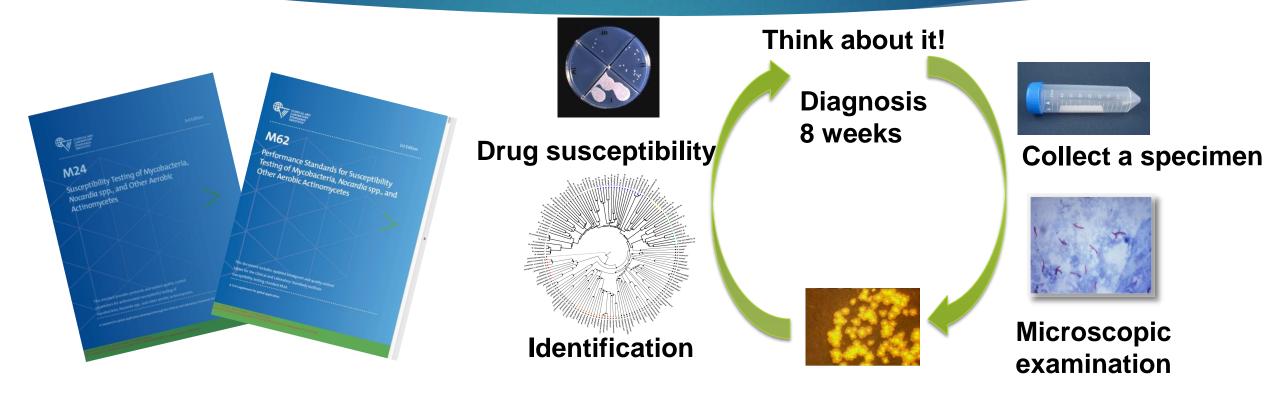
NTM Pulmonary Disease: Diagnostic Criteria

Clinical	Pulmonary or Systemic Symptoms	
Radiological	Nodular or cavitary opacities on chest radiograph or HRCT that shows bronchiectasis with multiple small nodules	Both required
Appropriate exclu	sion of other diagnoses	
Microbiological	 Positive cultures from at least two separate sputum samples. If the resund nondiagnostic, consider repeat repeat sputum AFB smears and cultures or Positive cultures from at least one bronchial wash or lavage or Transbronchial or other lung biopsy with mycobacterial histologic feat (granulomatous inflammation or AFB) and positive culture for NTM or bid mycobacterial histologic features (granulomatous inflammation or AFB) sputum or bronchial washings that are culture positive for NTM 	tures ppsy showing



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

Diagnosis of NTM Infections: Laboratory Diagnosis



Culture (liquid and solid media)



Antimicrobial Susceptibility Testing

Species	Drugs					
·	Rifampicin		AS	ST for M	IAC	
M. kansasii	Clarithromycin*			Μ	IC, ug/ı	ml
			Antimicrobial Agent	S	I	R
MAC	Macrolide		Clarithromycin	≤8	16	≥ 32
	Amikacin		Amikacin (IV)	≤16	32	≥64
			Amikacin	≤ 64	_	≥ 128
M. abscessus	Macrolide		(liposomal inhaled)			
	(including erm(41) gene) Amikacin					

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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

THIS OFFICIAL STREEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS	in earlier standards to allow the reader a great- er opportunity to assess the scientific basis	ner but in low numbers, then multiplies it the hospital heating tanks where the temper
BOARD OF DERICTORS, MARCH 1990.	for ideas and recommendations that are put	ature is 43° to 45° C, the optimal tempera
	forth. Included within this statement are the first recommendations of diagnostic criteria	ture for growth of this organism (16). Pre- sumable, aerosolization of the organism the
Contents	that apply orignarily to the NTM and the first	results in infection in the susceptible host
Introduction	American Thoracic Society (ATS) recommen-	Much less is known about the environmenta
Epidemiology/Pathogenesis	dations of specific therapestic drug regimens	erideniology and sources of infection for the
Clinical Presentation and Diagnostic Criteria	for disease caused by M. kensusii and M. evi-	other NTM, although environmental source
Laboratory	sim complex.	of infection are likely. A good review of en
Treatment of M. kunsesi Disease	It is anticipated that additional changes will	vironmental studies is provided by Wollnsk
Treatment of M. aviave Complex Disease	occur with the NTM. More species will be	and Rynearson (2)
(M. anium, M. intracellulare, M.	recognized, additional information about	Much remains to be understood about th
acrodulaceum)	treatment will be accumulated, and some con-	pathogenesis of NTM infection and diseas
Treatment of Rapidly Growing	cepts about these organisms may change. Un-	in humans. Epidemiologic studies and skie
Mycobacterial Disease	til that time, this statment should supplement	tost surveys suggest that person-to-person
Treatment of M. marinaw Disease	existing literature regarding diagnosis and	transmission of infection is rare. It is assume
Treatment of Other Nontuberculous	therapy of these resonancerial diseases.	that most persons are inflicted by environment
Mycobacteria Pulmonary Disease		tal NTM. Of the likely sources of infection
Monitoring for Drug Toxicity	Epidemiology/Pathogenesis	airborne NTM may play an important rol-
Summary	Sources of Infection	in respiratory NTM disease, whereas ingest
January 1	Most NTM are isolated from water and soil	tion of NTM may be the source of infection
	(0. 2), but some are isoketed from other sources.	for children with NTM cervical lymphadeni tis and for patients with AIDS whose dissers
Introduction	such as house dast (3). Extensive environmen-	to and for patients with AIDS whose disserts instead M. avour disease may begin with gas
This is the first official statement of a diag-	tal studies in the United States have shown	trained M. avour disease may begin with gas traintestinal infection. It is not known whether
nostic and therapeutic standard that deals ex-	that M, aviase complex grows will in natural	NTM disease develops soon after infection
clasively with the nontuberculous myophac-	waters, particularly in the Southeast (4). M.	or, like taberculosis, develops after a perior
teria. This topic was previously covered briefly	aviaw complex strains with plaunids, possi-	of latent infection. Direct inoculation with
in the statement on "Diagnostic Standards and	bly associated with viralence, have been shown	NTM creanisms in the water or other mate
Classification of Tuberculosis and other	to be prefermially amosolized, providing a	rial is likely the source of infection for pa
Mycobacterial Diseases," the fourteenth and	possible mechanism for sirborne acquisition	tients with soft tissue infectiors.
most recent version of which was published	of these organisess (1). Although M. evium	
in 1981. Historically, M. tuberculosis, M. bo-	is an important cause of disease in poultry and owing, serologic studies have not indicat-	Parasiance in Humans
vis, and M. Jeprar have caused the prepos- derance of human disease. However, in re-	and owine, serologic intactes rave not installa- of that animal, to human transmission is im-	Although first observed soon after Keyli's die
cent years, other mucchacteria have become	portant in human acquisition of infection (6).	covery of the tabercle bacillas, NTM were no
more widely appreciated as potential human	It is now amorally accritical that previoumen-	widely recognized as human pathogens und
nathoams, Collectively, these mycobacteria	tal sources, expecially natural waters, sre the	the 1950s when several large series of patient
have been identified by a variety of terms, in-	reservoir for most human infections caused	with NTM disease were reported (37-19)
chading mycobacteria other than tubercle	by M. enhant complex.	These patients were opidemiologically distinct
bacilli, environmental enveobacteria, "atyri-	Water is also the likely source of infection	from patients with taberculosis, being older
call monthecteria, and montherculous myon-	for M. merimon, commonly associated with	more commonly white, and quite often with
bacteria (NTM).	fish tanks and swimming pools (7). In con-	underlying chronic lung disease such as bross
The tremendous growth in the number and	trant, M. kamaati has not been recovered from	chiectasis, silicosis, and healed tuberculosis
prevalence of these species, which we have	soil or natural water supplies (2). It has been	Positive reactions of 10 mm or more to put
elected to refer to collectively as the NTM,	isolated on numerous occasions from tap wa-	Ged proteis derivative (PPD) toberralin wer
has prompted us to put forth this new state-	ter (8) and from a few domestic animals. Rap-	less common than among tuberculous pa
meet. The principles of therapy and diagno-	idly growing reprobatteria such as M. fortui- ture M. chelonge, and M. speremetic can be	tierrs, and family contacts tended to be tabenulin-negative.
sis of disease caused by M. raberculosit have been updated since the 1980 statement and	num, M. cherowar, and M. swegmans can be multily recovered from soil and natural water	As reports of patients with NTM diseas
now appear in two separate statements. "Theat-	readily recovered from soil and natural water supplies, and investigations of some nonoco-	increased, it became apparent there was
most of Taberculosis and Taberculosis Infec-	mial outbreaks caused by these species have	marked geographic variability both in the
tion in Adults and Children" (American Re-	supported that air (9, 10), tao water (11-13),	prevalence of decase and in the prochasteria
view of Respiratory Disease 1986; 134:255-631	and distilled water used for dialwis (14) or	species responsible for disease. Most patient
and "Diagnostic Standards and Classification	preparing surgical solutions (e.g., pretian vin-	in the southmastern United States with NTN
of Tuberralasis" (American Review of Resei-	(et) (15) may serve as the source of the organ-	disease were from rural areas and had iso
ratory Disease 1990; 142:725-35). Like the	iams. M. amore has been recovered almost	lates of M. evium complex, whereas those is
previous standards that dealt primarily with	exclusively from water, expecially from hot	the central United States more commonly has
tuberculosis, this statement is designed as a	water taps within the hospitals where it has	disease caused by M. kannaril (20).
basic guide for those professionals involved	been associated with cases of clinical disease	In addition, patients with NTM disease
in the diagnosis and managment of disease	(16). Interestingly, the organism has not been	tended to react more strongly to skin test an
caused by NTM. Although not prepared as	recovered from water mains entering the hos-	tigens prepared from the infecting myoobac
an all-inclusive review, the areas of discus-	pital. However, it has been speculated that	terial species than to standard PPD-5 or PPD
sion have been referenced in more detail than	the organism enters the hospital in this man-	T, antigens prepared from M. tabercalosi

American Thoracic Society

Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria

1997

SUMMARY	tion including commercial DNA probes (M. assium co
Diagnostic Criteria of Nontuberculous Mycobacterial Long Disease in HIV-Seropositive and -Seronegative Hosts	plex, M. kamadi, M. gordenae) and high-pressure lisp chromatography are preferred over the slower tradition biochemical methods.
The following criteria apply to symptomatic patients with in- fittane, nodular or coritary disease, or a high resolution com- pared tomography scan that shows multiBocal heusehiectanis and/or multiple small tooklas.	 Susceptibility testing of M. avium complex. Susceptibilitistic statistics with rifation and the antisuberculouis drugs in mecommended. Routine testing against chartherenychi show not be performed as but that test who also be deformed as a set of the result.
A. If three spatian/bronchial work results are available from the previous 12 size. three positive cultures with negative AFB smear results or 2, two positive cultures and one positive AFB samear. 	Jates from patients who have failed prior macrolide there or prophylasis. Misimal inhibitory concentration (MIC) > 32 µg/ral is the recommended maintance breakpoint. 4. Susceptibility nating of M. Jassanii. Routine susceptibility insting of M. Jansenii should include out of Reprint. Seen
B. If only one heusehial wash is available: L positive culture with a 2+, 3+, or 4+ AFB seasor or 2+, 3+, or 4+ growth on solid media	currently used resistance breakpoints for isoniazid a streptionycii often give mikeading results and methods the other drugs have not been established. 5. Susceptibility initia of the gand provers. Susceptibility in
 If spatientheorehial work evolutions are reading-testic or sandher theorem course its excluded. transless observations of the standard of the original standard of the standard of the standard of the ignoralismous influenzation and/or APII and one or more spatiants of heurichial workings are positive for an NTM result for mathematical standards. 	ing of clinically applicant rapidly growing reproduct (M. Greinsmith, M. alternaux, M. christwark should not performed with the anitudecredusia agreen. They should invested application astrohowical draps including agriculture of the independent of the fluctuation of quinekness, a suffice mide, reduction, and claritheromycta.
Comments	PROPHYLAXIS AND TREATMENT OF NONTUBERCULOUS MYCOBACTERIA DISEASE
These criteria fit best with M-avian complex, M-absonue, and M-Avanani. Two little is known of ather NTM to be ow- tain how applicable these criteria will be. At locat these requiratory samples should be evaluated from each patient. Other massaultic causes for the disease should be eachided. Equer consultation should be singlit when diagnostic efflications are seconstreted.	 Tractover of M. kannali packennary themes: A regimen- dary toorisated D00 mgi, riferenzin 000 mgi, and theme and D2 mgbg for 2 ms, then I mgbg for 18 ms with minimum of 12 mo enhance mgativity is recommended. The recommendation of the second second second second information or riferentia with second to be understand enhanced in HIV positive partients who take prostase informa- tions.
KEY LABORATORY FEATURES OF THE NONTUBERCULOUS MYCOBACTERIA	Treatment of M. avium complex publicousty disease. A re- men of daily clarithromycin (500 mg twice a day) or with
 Sinthig and enhore Carrars methods of spectrum stating and exhres used for M. It derivations are screptial for mann (NTM spectra. The preferred methodology includes Baneschrener survaying out cohere in larged a soluture and well as one Muldihelsonik. (PHI to ar 1111) agar. Spectras for responsible for curasses of doors, which well have branc- buston temperatures, and the relatively familianes spectra M. Samesphalton, M. guesseens, and M. Goognaraux. Spectra shuffitzabare. Methods of rapid spectra theofflow Anisopy Officerum Vol. 16, pp. 13–15, 1979 	mysin (256 mg), ritinging 100 mg) or eithenini (200 m and echamizated (25 mg) kg ke 2 van ches 15 mg) kg in 2 van Schele for therapy of solution not integrated with the 15 oran Schele for therapy of solution and integration of the 15 considered for the first 1 what an integrated ratio of the last transmission of the first 1 what an integrated ratio of the 15 mg mg solution of the 15 mg solution of the 15 mg mission of the 15 mg ratio of the 15 mg solution of the integrated sufficiency of the 15 mg solution of the 15 mg solution into a design or antherapyoint (250 mg solution of the 15 mg solution and 13 mg mg pg ratio. Cranadizations should be given the addition of a theid day geneficiably efficient as a dimension dimension.

2007

American Thoracic Society Documents

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

Griffith, Timothy Alsamit, Barbara A. Brown-Ellott, Ar 4. Holland, Robert Horsburgh, Gwen Hultt, Michael F. Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., a brief Divenses Subcommittee

Am | Brogar Crit Care Med. Vol 175, pp 347-416, 2007 DOI:10.1104/nom.200604.07137 Internet address

Treatment of nontuberculous nycobacterial pulmonary disease; an mycobacterial putmonary useeses an official ATS/ERS/ESCMID/IDSA clinical practice guideline

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¹⁰¹ DECEMPENDING dated proto publics product it enhances date in first summer of complexity symphotoxic (OTM) planary date

Consensus management recommendations for less common @ 10 non-tuberculous mycobacterial pulmonary diseases

2022

i Lange, Enk C Bitti get, Errmanvelle Combax, DavidE Griffich, Lor K Marnes, Kenneth'N Olivier, Miguel Santin, Jeson E Stovic, Errico

2020

IDSA FEATURES

MDSA hvma

A CARRENT (XXXXX) + (

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical

Practice Guideline: Executive Summary

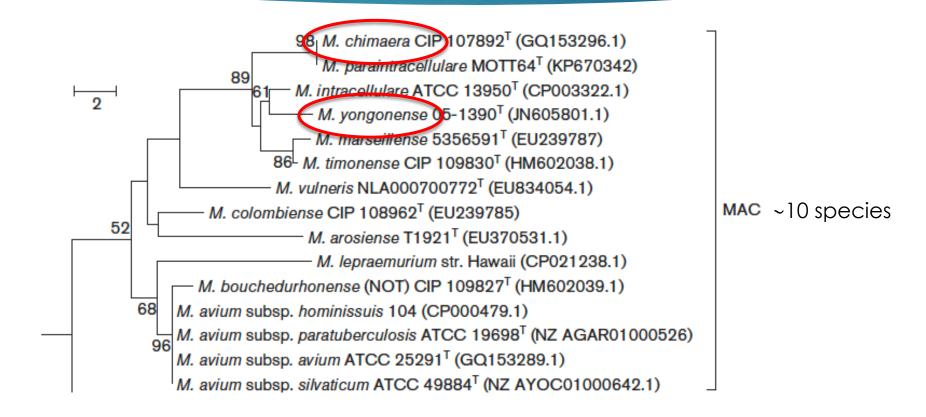
Review

The 2020 clinical practice evideline for the treatment of non-tuberculous microbacterial put The deviation process process of the transmission on the environment of the second sec it the treatment of seas common case of the brought uidance for pulmonary diseases caused by seven additional organisms: Mycobacterium cholonae, Mycobacteria obacterium genarense, Mycobacterium genarense, Mycobacterium genarense, Mycobacterium genarense, Myco ption of M malma eports and case series. For M malmorese, results from two rat studies provided a better evidence base for treatment recommendations, although the evidence was still

The 2020 updated management guideline for patients. Mycobacterians similar, and Mycobacterians sculpai, with non-tuberculous mycobacterial pulmonary diseases. The following consensus guidance includes record with non-tubreuknes mychacierial painnawy disease. The following consensus guidance includer 07/04/PU focus on population, intervention, intervention, intervention, and outcome quantion-guided by in-service sum partners, and concome quantion-guided management bility results. With the exception of M dollars wormendeduction for milwynamic donase in adults, and adult adult adult adult of M dollars of M dollars and the second or pulmonary disease anium complex, Matcha fam ampi, and Mycobasterium altoceas." mins sampt, and Mijohadrahum ankonisi." used tot the organism consultation there, management optimism for NTAPO is used by micially relevant non-subscrubau mijohackim (Methods) even in the previous management galaditien are. A search (see appendic pp +7) was adapt del for the caso of affected patients: At present, renorminations for patients with other NTM— of Print. In Privots, 6 (Ohen Non-Ins. Insumers incommendations for patients with other NTM of Prints. In-Process PDF are primarily liked on operturbations and other translationary particular of patients with other NTM of Prints, and the Code variable are produced on the patient of the NTM of Prints and Section were base operations in distinguishing and the same patient of the Section of Prints and Section 2018 and the Section of the Section of Section 2018 (Section 2018) and the Section 2018 and the Section 2018 and the Section 2018 and the distinguishing and the Section 2018 and the Se Diseases Society of members of the 2020 ATS, ERS, ideline committee did syste-erature, independently of the original task force, to provide

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





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	
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin) ^b	Daily (IV aminoglycoside may be used 3 times weekly)	12 months beyond culture conversion

a. Alternative drugs could include clofazimine, fluoroquinolones, linezolid (tedizolid), bedaquiline

b. Consider for cavitary, extensive nodular bronchiectatic or macrolide resistant disease

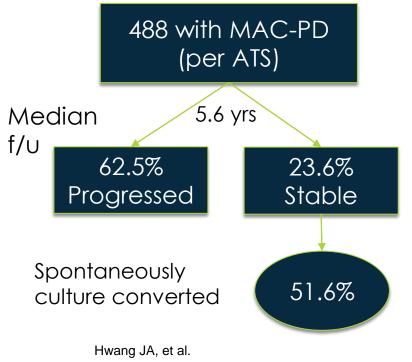
Daley CL, et al. CID 2020;71:905-913 and Euro Respir J 2020;56:2000535

Guideline recommendation

In patients who meet the diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting, <u>especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease</u> (conditional recommendation, very low certainty in estimates of effect). Daley CL, et al. *CID* 2020;71:5-913; *Euro Respir J* 2020;56:2000535

Guideline recommendation

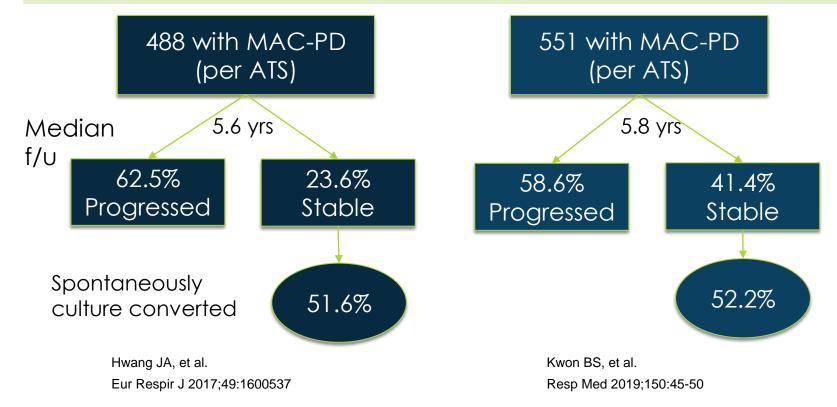
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Eur Respir J 2017;49:1600537

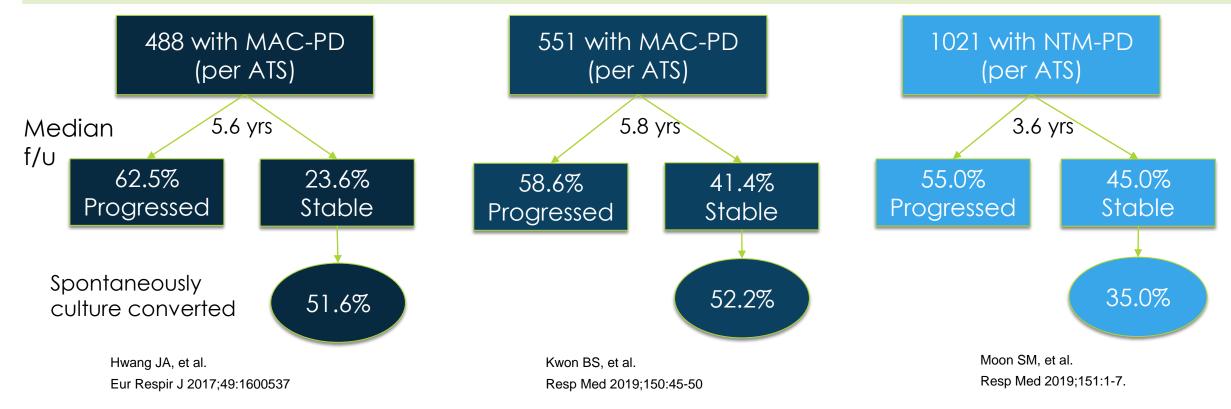
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Risk Factors Associated with Progression

Host/Demographic Factors

- Male gender
- Older age
- Presence of co-morbidities
- Low body mass index

Laboratory Factors

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

Radiographic Factors

- Fibrocavitary
- Extent of disease

Microbial Factors

- Bacterial load
- Species



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**

lational Jewish

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Health

Lifestyle modifications



Best choice is what the patient will do

- Education
- Time commitment

Treatment Outcomes for MAC

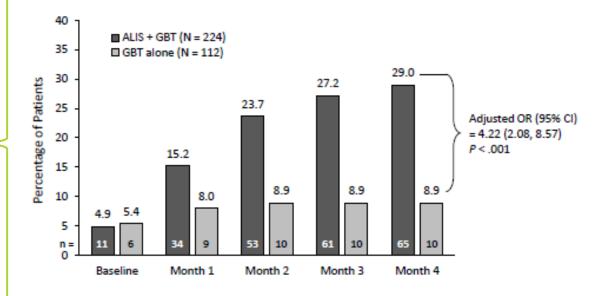
	Culture Conversion	Microbiologic Recurrence	Reinfection		
Macrolide susceptible					
Non cavitary Cavitary	70% - 80% 50% - 80%	25-48%	46-75%		
Macrolide resistant	Macrolide resistant				
No surgery/aminoglycoside* Some surgery/aminoglycoside Surgery + prolonged aminoglycoside*	5% 15% 80%	-	—		

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 guidelinebased 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

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

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		

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



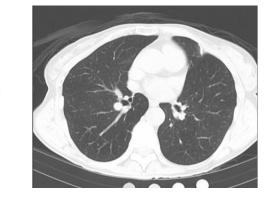
Surgery Plus Medical Therapy or Medical Therapy Alone?

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

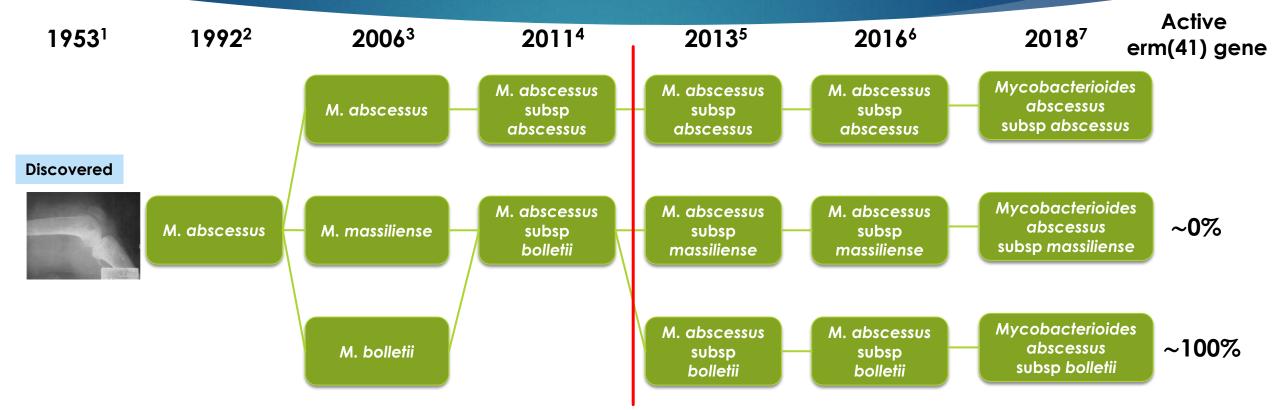






Daley CL, et al. CID 2020;71:5-913 and Euro Respir J 2020;56:2000535

Mycobacterium abscessus An Evolving Taxonomy



¹Moore M J Invest Derm 1953;20:133 ²Kusunoki S. Int J Syst Bacteriol 1992;42:240 ³Adekambi T. Int J Syst Bacteriol 2006;56:133 ³Adekambi T. Int J Syst Bacteriol 2006;56:2025 ⁴Leao SC. Int J Syst Evol Microbiol 2011;61:2311 ⁵Cho YJ. PLoS ONE 2013 8(11):e81560 ⁶Tortoli E. Int J Syst Evol Microbiol 2016;66:4471 ⁷Gupta 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 Sus	ceptibility					
Mutational	Inducible	No. of Drugs	Preferred Drugs		Frequency of Dosing	Treatment Success
Susceptible	Susceptible		Parenteral (choose 1-2) Amikacin Imipenem (or cefoxitin) Tigecycline	<i>Oral (choose 2)</i> 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			

Recommended Treatment Regimens M. abscessus – A Phased Approach

Macrolide Sus	ceptibility					
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	<i>Oral (choose 2)</i> Azithromycin* Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	> 80%
		Continuation Phase ≥ 2	Oral/inhaled (choose 2-3) Azithromycin* Clofazimi Linezolid Inhaled an			
Susceptible	Resistant	Initial Phase ≥ 4	Parenteral (choose 2-3) Amikacin Imipenem (or cefoxitin) Tigecycline	<i>Oral (choose 2-3)</i> Azithromycin** Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides	<40%
		Continuation Phase ≥ 2	Oral/inhaled (choose 2-3) Azithromycin** Clofazin Linezolid Inhaled	nine amikacin	— Weak Regin	nen!

*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 Sus	ceptibility				
Mutational	Inducible	No. of Drugs	Preferred Drugs	Frequency of Dosing	Treatment Success
Susceptible	Susceptible	Initial Phase ≥3	Parenteral (choose 1-2)Oral (choose 2)AmikacinAzithromycin*Imipenem (or cefoxitin)ClofazimineTigecyclineLinezolid	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)Oral (choose 2-3)AmikacinAzithromycin**Imipenem (or cefoxitin)ClofazimineTigecyclineLinezolid	Daily (3 times weekly may be used for aminoglycosides	<40%
		Continuation Phase ≥ 2	Oral/inhaled (choose 2-3) Azithromycin** Clofazimine Linezolid Inhaled amikacin	— Weak Regir	nen!
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	Ν	Sputum conversion	Failure to convert	Recurrence*
Koh,	Non Cystic	M. abscessus	24	25%	58%	17%
2011	Fibrosis	M. massiliense	33	88%	3%	9%
Lyu,	Non Cystic	M. abscessus	26	42%	27%	31%
2014	Fibrosis	M. massiliense	22	96%	0%	5%
Roux, 2015	Cystic Fibrosis	M. abscessus M. massiliense	12 7	25% 86%	-	- -
Park, 2017	Non Cystic	M. abscessus	19	26%	74%	55%
	Fibrosis	M. massiliense	17	82%	18%	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 ± betalactamase inhibitors
- Cycline derivatives
- Rifabutin (for M. abscessus)
- Apramycin

New Drugs

- Epetraborole
- SPR720

New Formulations

- Inhaled tigecycline
- Inhaled clofazimine

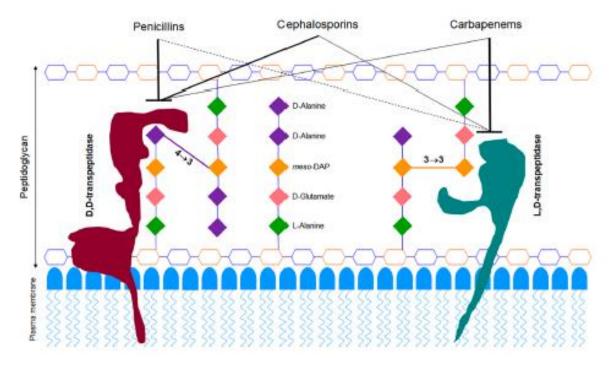
Nonantimicrobials

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

Mycobacterium abscessus and β-lactamase Inhibitors

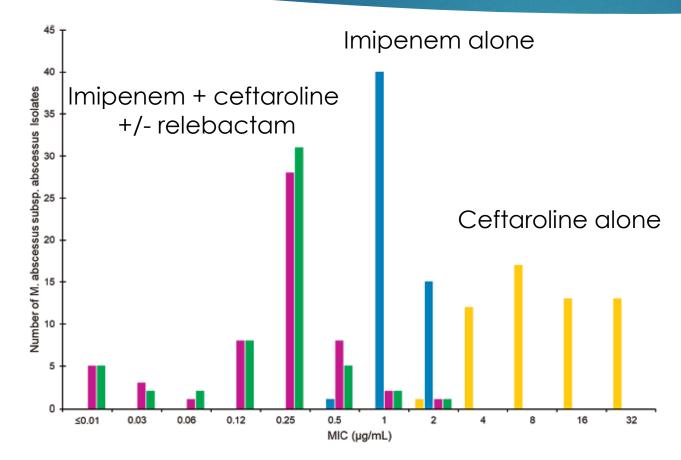
- Mycobacterium abscessus produces a broad spectrum β-lactamase (Bla_{Mab})
 - Imipenem and cefoxitin are slowly hydrolyzed by Bla_{Mab} which contributes to their efficacy
- Inhibition of Bla_{Mab} by avibactam improves the efficacy of imipenem against M. abscessus in vitro, in macrophages and zebrafish 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

- Ceftaroline ■Imipenem ■Imipenem + Ceftaroline 1 μg/mL ■Imipenem + Ceftaroline 1 μg/mL + Relebactam 4 μg/mL

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

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

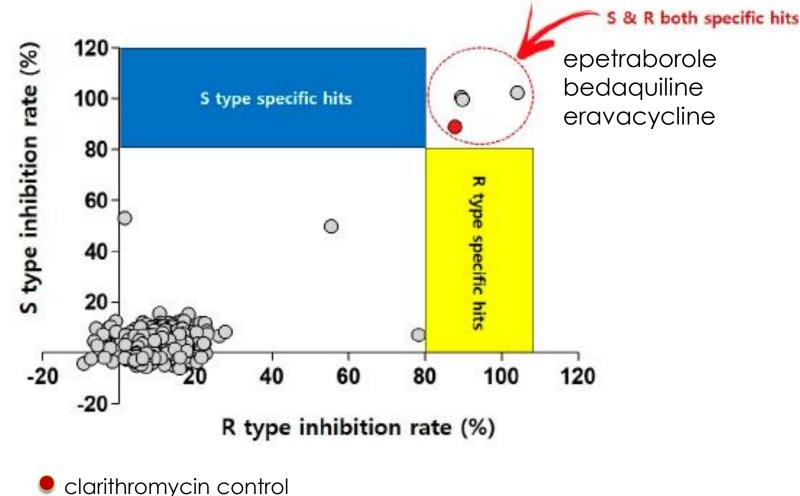
Omadacycline M. abscessus Case Series

Study (date)	Ν	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			

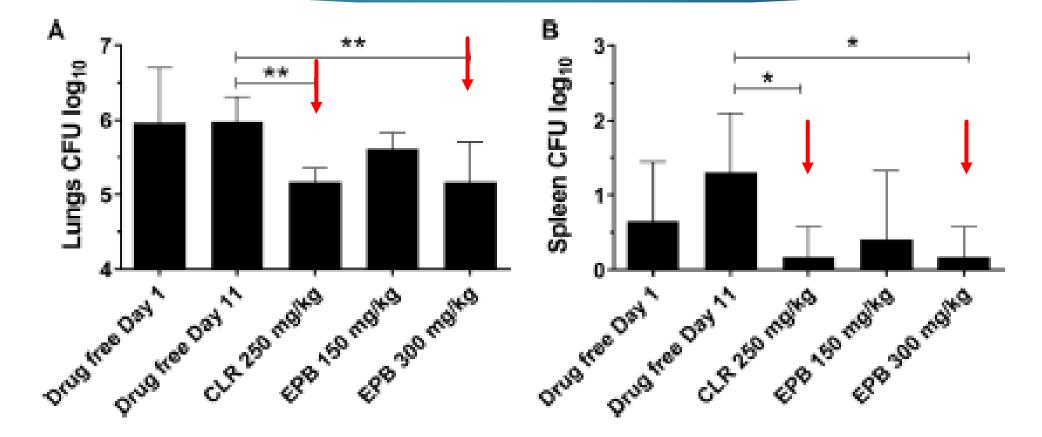
Activity of Epetraborole in M. abscessus

OH OH OH NH₂ Epetraborole

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



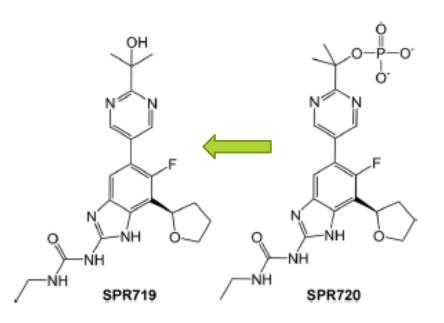
Epetraborole Has Similar In Vitro Activity as Clarithromycin Against M. abscessus



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

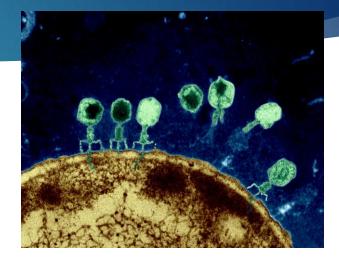
NTM species	MIC range (mg/liter)	MIC ₅₀ (mg/liter)	MIC ₉₀ (mg/liter)
MAC (n = 73)	0.06-4	1	2
M. kan sasii (n = 21)	<0.03-0.25	<0.03	0.125
M. abscessus (n = 32)	1 to >32	2	8
M. simiae (n=4)	2-8	NA	NA
M. malmoense (n = 3)	0.06-0.5	NA	NA
M. xenopi (n = 5)	0.06-0.5	NA	NA

^aMAC, M. avium complex; NA, not applicable.

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

Bacteriophage

- Bacteriophage Virus that infect bacteria
- Phages are the most abundant organisms in the biosphere - 10³¹ phage with entire population turning over every few days
- Genomically, small, old and diverse
- Anecdotal reports of successful treatment for resistant microbes



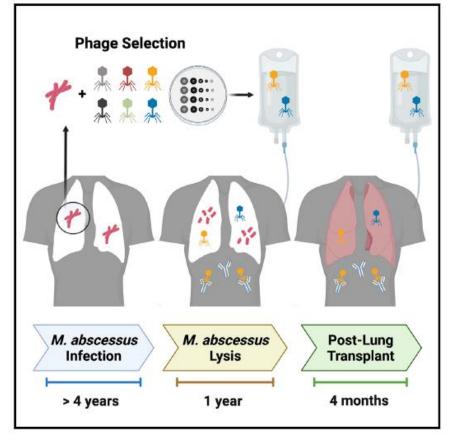


Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktalis To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection

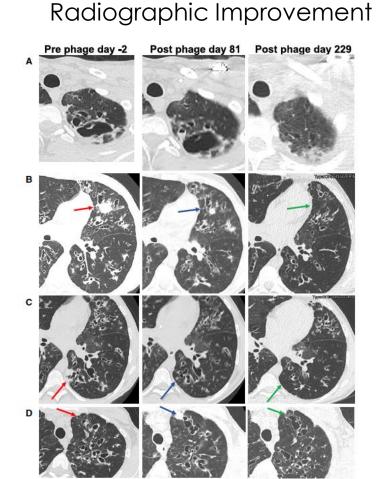
Robert T. Schooley» Biswajit Biswas, hc Jason J. Gill, de Adriana Hernandez-Morales, Jacob Lancaster, * Lauren Lessor, * Jeremy J. Barr, 9-% Sharon L. Reed, ^{a,b} Forest Rohwer, 9 Sean Benier, 9 Anca M. Segall, 9 Randy Tapilitz, * Davey M. Smith, * Kim Kerr, * Monika Kumaraswamy, * Victor Nizet, ¹ Leo Lin, ¹ Meianie D. McCauley, * Steffanie A. Strathdee, * Constance A. Benson, * Robert K. Pope,* Brian M. Leroux,* Andrew C. Picel,* Altred J. Mateczun,^b Katherine E. Cliwa,ⁿ James M. Regelmbal,^b Luis A. Estrelia,^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,^{a,v} Theron Hamilton^b

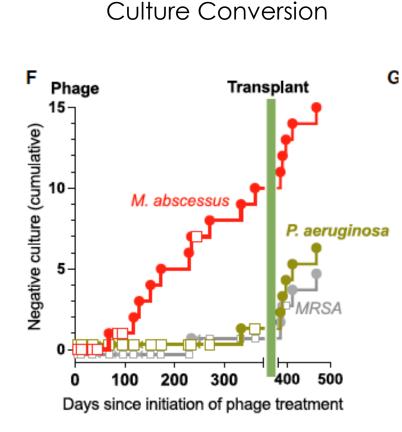
Mycobacteriophage Therapy for M. abscessus

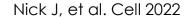
- 26 year old man with cystic fibrosis
- Chronic MRSA and Pseudomonas aeruginosa infections
- Treated for MAC lung infection 5 years earlier
- M. abscessus subspecies abscessus isolated
- Treated with 4 to 5 drugs for over 4 years
- Remained culture positive with declining FEV1

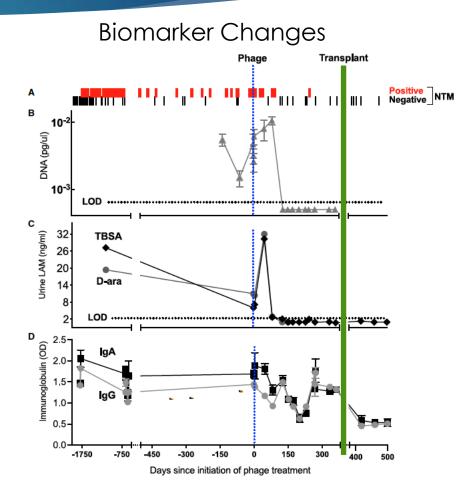


Treatment Outcomes with Phage Therapy









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 Apramycin	Bedaquiline	Amikacin liposome
	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	