The management of *Rapidly Growing Mycobacteria*

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Disclosures

- Insmed: Speaker, Advisory board, Investigator
- Paratek Pharmaceuticals: Speaker, Advisory board
- AN2 Therapeutics: Advisory board
- Renovion: Investigator

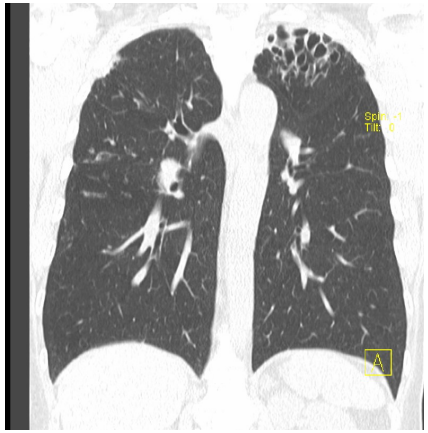
M. abscessus pulmonary disease is heterogenous

64-year-old female

Smear -

Culture *+ M. abscessus*

Diagnosis 2016

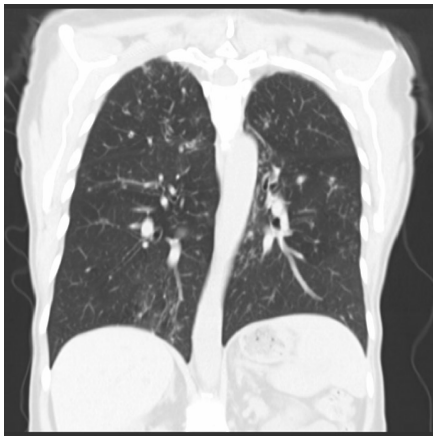


64-year-old female

Smear -

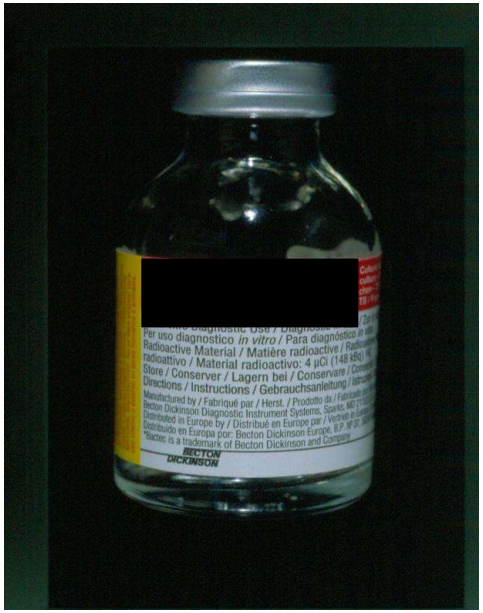
Culture + *M. abscessus*

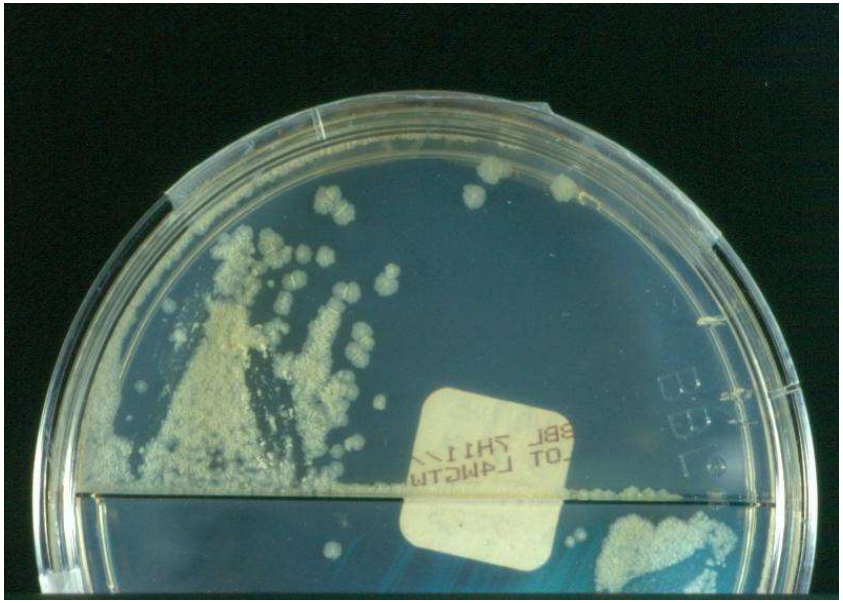
Diagnosis 2013



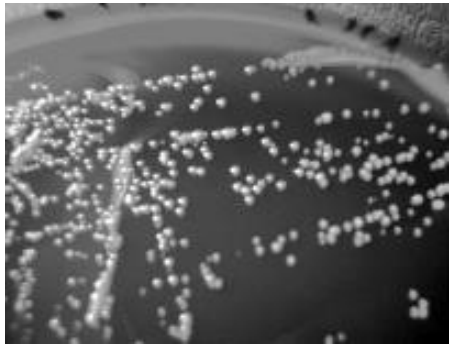
Rapidly growing mycobacteria

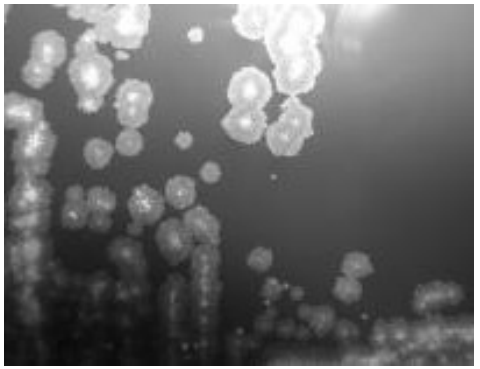
In vitro rapid growth in subculture (usually 3 to 10 days)





M. abscessus



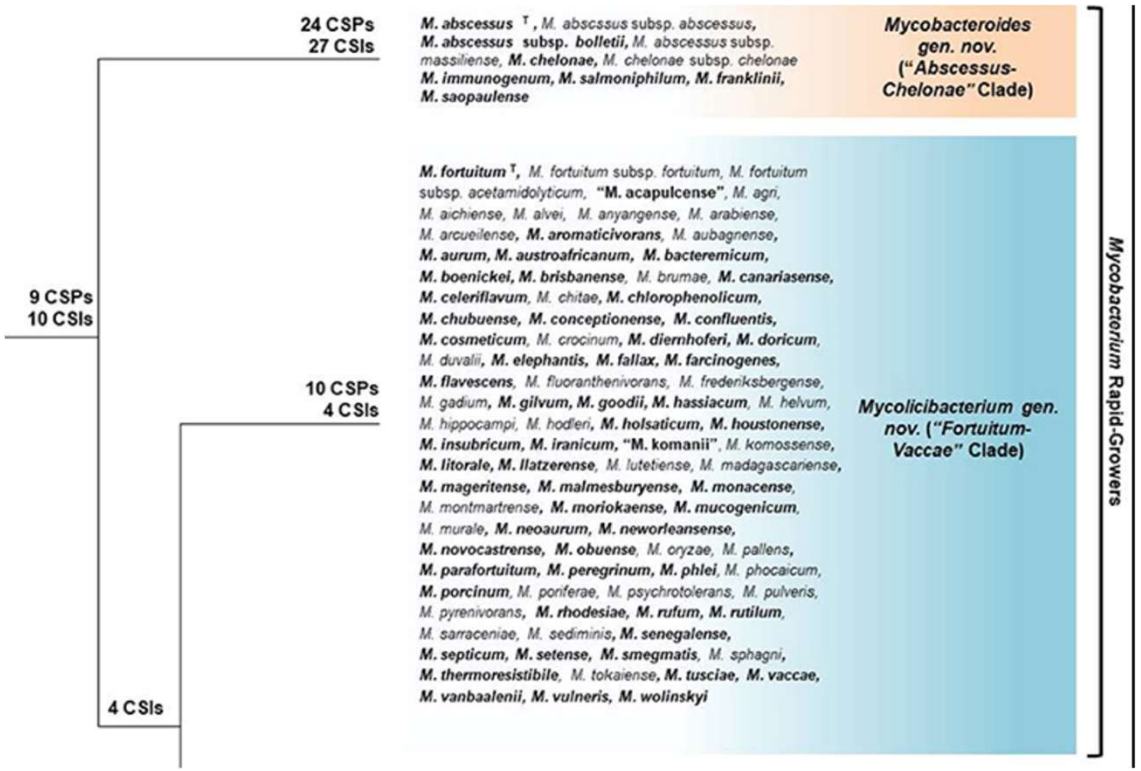


Smooth phenotype

Rough phenotype

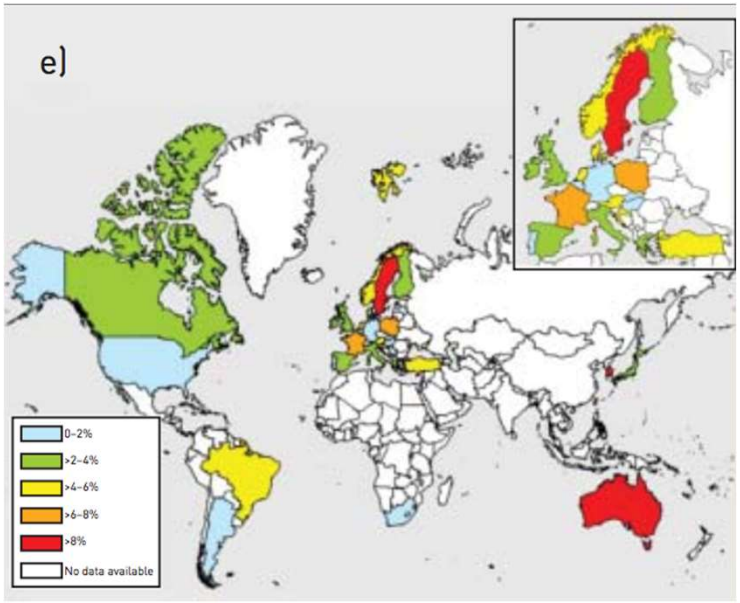
J Clin Microbiol 2007;45;1497-1504.

Phylogenomics and Comparative Genomic Study



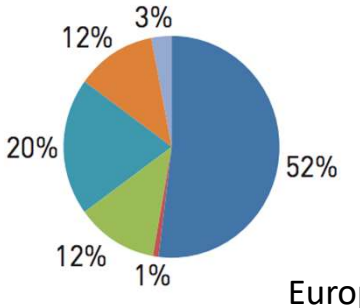
Gupta RS, et al. Front Microbiol. 2018 Feb 13;9:67.

Geographic distribution of NTM isolates: 2008

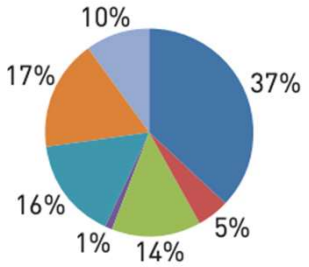


Distribution of NTM
- MAC
- *M. kansasii*
- *M. xenopi*
- *M. malmoense*
- RGM
- *M. gordonae*
- other SGM

N. America

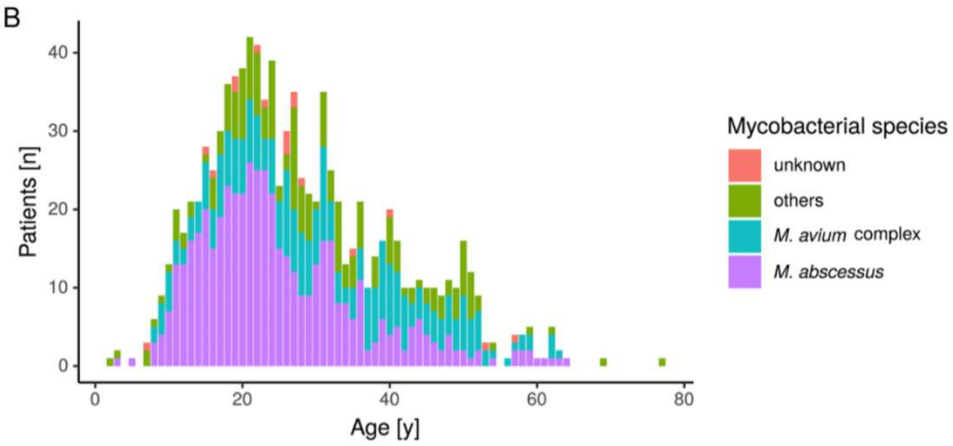


Europe



Eur Respir J. 2013 Dec;42(6):1604-13.

Distribution of *M. abscessus* in CF cohorts (2020)

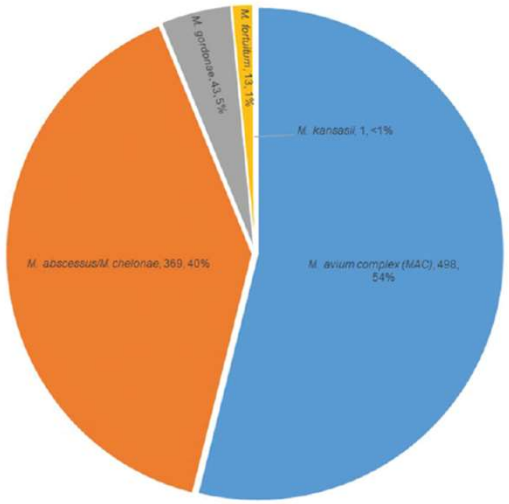


2020 German CF registry data

n=6295

3% positive NTM sputum cultures

56% *M. abscessus*



2020 US CF registry data

n= 10,220

10% positive NTM cultures

40% *M. abscessus*

Microbiology spectrum. , 2022, Vol.10(4), p.e0171422

US CF Registry Database 2020

Distribution of *M. abscessus* subspecies recovery

- Int J Tuberc Lung Dis 2014;18:1141

Author (yr)	Country	No.	*Subspecies abscessus*	*Subspecies massiliense*	*Subspecies bolletii*
Zelazny (2009)	USA	40	67.5%	27.5%	5%
van Ingen (2009)	Netherlands	39	64%	21%	15%
Roux (2009)	France	50	60%	22%	18%
Harada (2012)	Japan	102	71%	26%	3%
Yoshida (2013)	Japan	143	63%	35%	2%
Nakanaga (2014)	Japan	115	60%	37%	3%
Huang (2013)	Taiwan	79	43%	56%	1%
Kim (2008)	Korea	126	53%	45%	2%
Koh (2011)	Korea	158	44%	55%	1%
Lee (2014)	Korea	404	50%	49%	1%

Macrolide Resistance: Implications for Treatment of *M. abscessus*

Clarithromycin susceptibility results					
Days 3-5	Day 14	Genetics	Subspecies	Susceptibility Phenotype	Use Macrolide
Susceptible	Susceptible	Dysfunctional erm(41) gene	*M. massiliense*	Macrolide susceptible	Yes
Susceptible	Susceptible	Dysfunctional erm(41) gene	*M. abscessus* (C28)	Macrolide susceptible	Yes
Susceptible	Resistant	Functional erm(41) gene	*M. abscessus* (T28) *M. bolletii*	Inducible macrolide resistance	Possibly but don't count as active
Resistant	Resistant	23S rRNA point mutation	Any	Constitutive macrolide resistance	Only for anti-inflammatory purposes

70%

Haworth C, et al Thorax 2017;72ii1-ii64

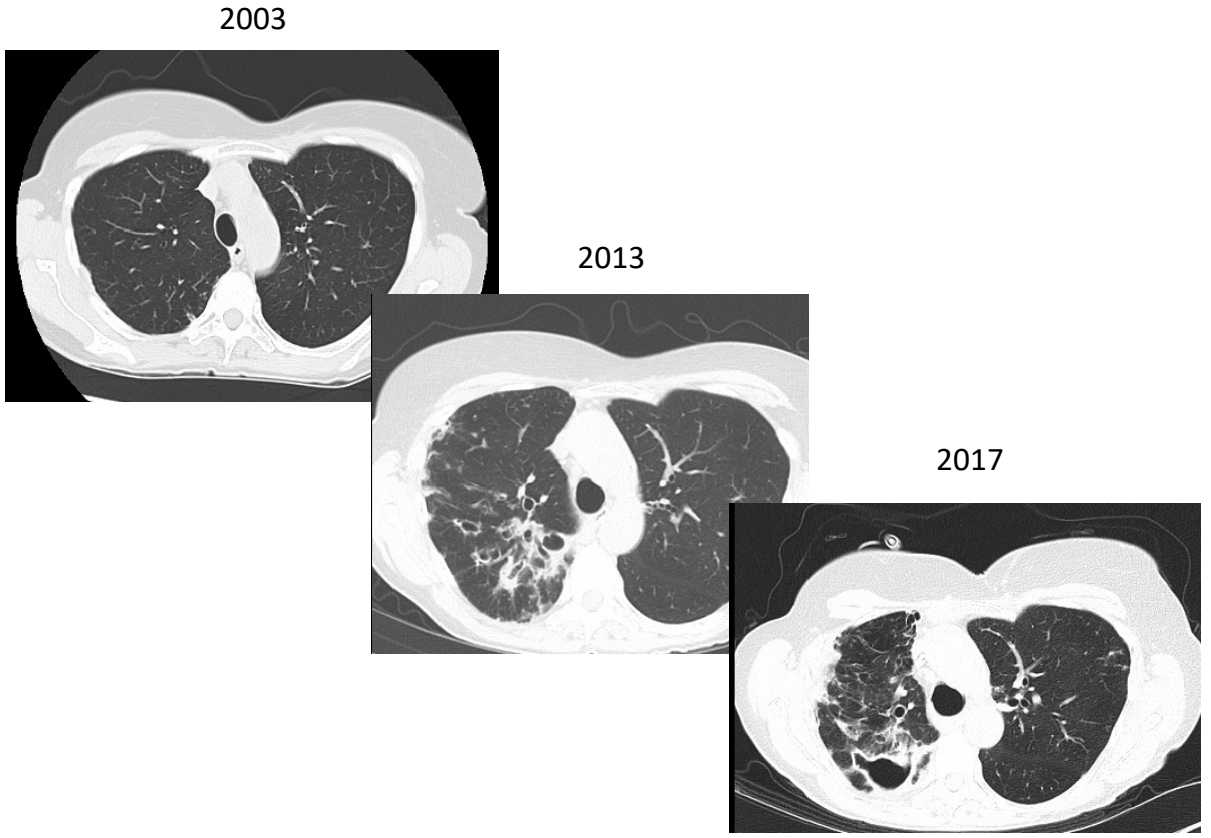
Antimicrobial Susceptibility Testing

Antimicrobial Agent	MIC, mcg/ml		
	S	I	R
Clarithromycin	≤ 2	4	≥ 8*
Amikacin	≤ 16	32	≥64

*extended incubation (14d) or molecular testing recommended to detect inducible resistance

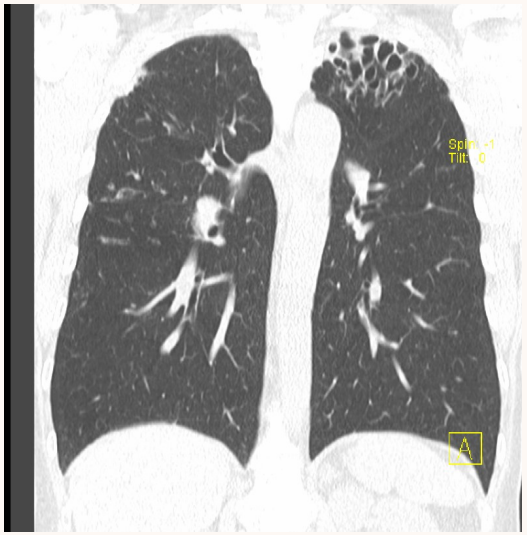
CLSI. M24S 3nd Ed. Performance Standards for Susceptibility Testing, 2018

Chronic Pulmonary Disease

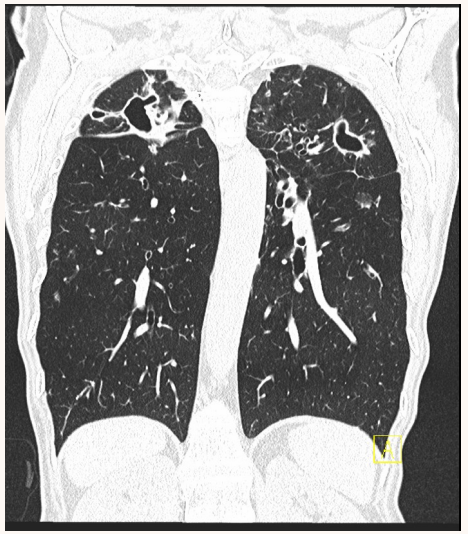


Follow up Cases

- 64-year-old female
- Smear -
- Culture *+M. abscessus*
- Heterozygote Delta F508
- C28, smooth morphotype
- No progression over 7 years



- 64-year-old female
- Smear -
- Culture + *M. abscessus*
- T28, rough morphotype
- Worsening cavitation



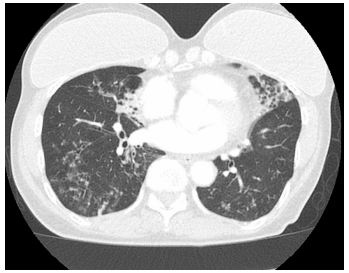
Predictors for Progression

N=113 median follow up 3.4 years, Seoul National University
~ 40 % progressed requiring treatment

BMI < 18.5 kg/m^2

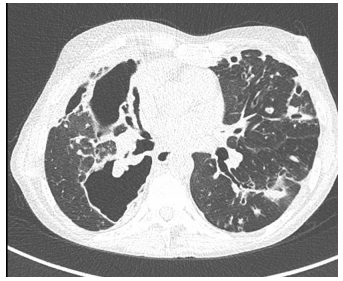
OR 4.79 (1.39–16.48)
p 0.013

Bilateral lung disease



OR 3.83 (1.06–13.82)
p 0.04

Cavitary lung disease



OR 3.62 (1.02–12.82)
p 0.046

Park J et al. CID 2017;64(3):301-8

Case

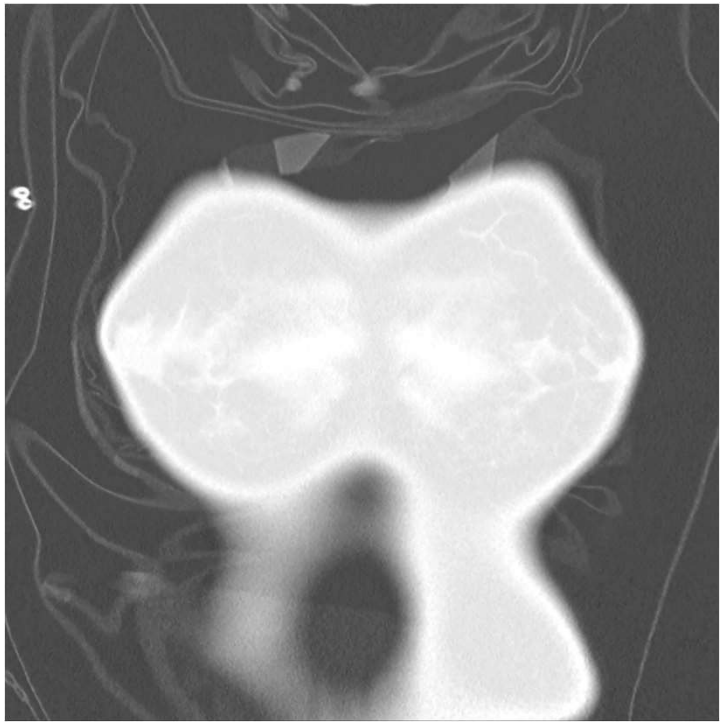
53- year-old female
Japanese descent, living in Hawaii

Chief complaint: severe chronic cough, weight loss
recurrent hemoptysis

Past medical history:
Bronchiectasis
Pulmonary MAC, per report
-Treated 4 mo (2023) azi/etham/rifampin/moxi/IV amikacin
GERD
G7P3

Medications: none

October 2023 CT chest



Case

- Review of outside cultures:
  - 1/2023, 7/2023 MAB
- 10/4/23, 10/5/23, 10/6/23
  - Smear +, Culture + >200CFU
  - *M. abscesssus* subspecies *abscessus*
  - A thymine at position 28 was detected consistent with inducible macrolide resistance
  - No mutations present in rrl or rrs

Mycobacterium abscessus ssp abscessus

MINIMAL INHIBITORY CONCENTRATION PANEL (NJH) (Preliminary)		
Amikacin	16 mcg/mL	**Susceptible**
Cefoxitin	64 mcg/mL	**Intermediate**
Ciprofloxacin	4 mcg/mL	**Resistant** [1]
Clarithromycin	0.5 mcg/mL	**Susceptible** [2]
Clofazimine	0.25 mcg/mL	**No Interpretation Available**
Doxycycline	>8 mcg/mL	**Resistant**
Imipenem	8 mcg/mL	**Intermediate** [3]
Linezolid	16 mcg/mL	**Intermediate**
Moxifloxacin	>4 mcg/mL	**Resistant**
Tigecycline	0.5 mcg/mL	**No Interpretation Available**
Tobramycin	16 mcg/mL	**Resistant** [4]
Trimethoprim/Sulfamethoxazole	>4/76 mcg/mL	**Resistant**

Note report is showing 3-day incubation

Manifestations of *M. abscessus* Pulmonary Disease

- Antimicrob Agents Chemother. 2018 Apr 26;62(5)

Characteristic	Resistant group (69)	Sensitive group (31)	P value
Cough, n (%)	55 (79.7)	25 (80.6)	0.914
Sputum, n (%)	69 (100.0)	31 (100.0)	1
Hemoptysis, n (%)	**22 (31.9)**	**4 (12.9)**	**0.045**
Bronchiectasis	66 (95.7)	29 (93.4)	0.655
Cavity	**50 (72.5)**	**8 (25.8)**	**<0.001**
Tree in bud	**16 (23.2)**	**14 (45.2)**	**0.027**

Recommended Treatment Regimens

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

*Azithromycin is active

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

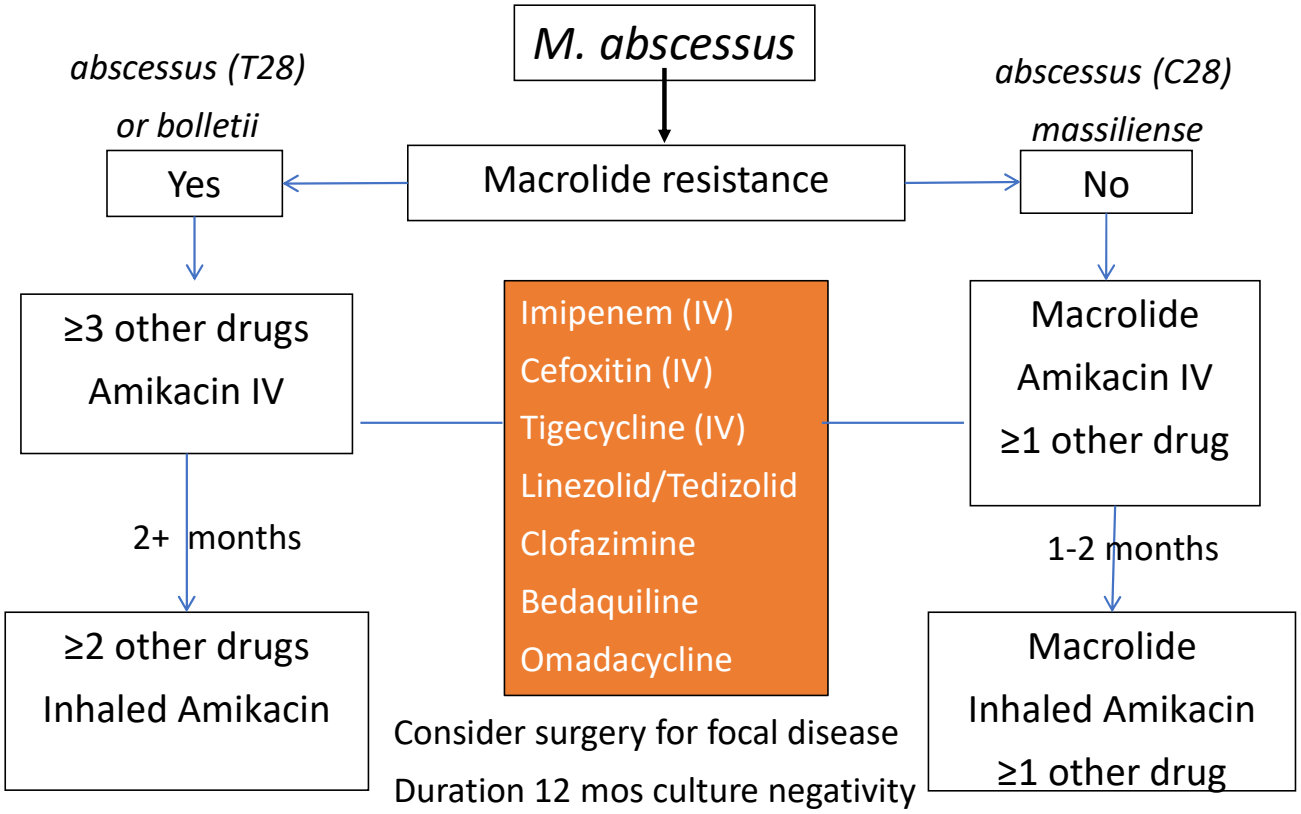
Recommended Treatment Regimens

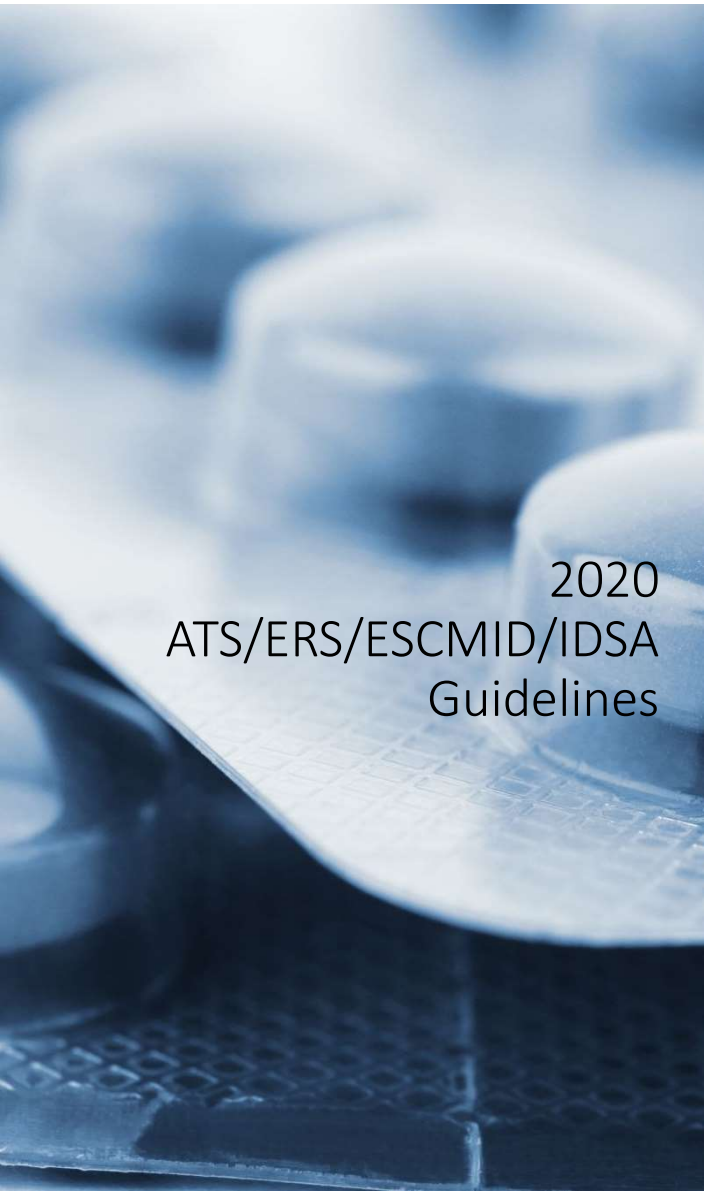
Macrolide Susceptibility					
Mutational	Inducible	No. of Drugs	Preferred Drugs		Treatment Success
Susceptible	Resistant	Initial Phase ≥ 4	Parenteral (choose 2-3) **Amikacin** Azithromycin** **Imipenem** (or cefoxitin) **Tigecycline**	Oral (choose 2-3) **Clofazimine** Linezolid	<40%
		Continuation Phase ≥ 2	Oral/inhaled (choose 2-3) Azithromycin** **Clofazimine** **Linezolid** **Inhaled amikacin**		
Resistant	Susceptible or Resistant	As above			<40%

**Azithromycin is unlikely to be active

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

Treatment of *M. abscessus*





2020 ATS/ERS/ESCMID/IDSA Guidelines

Without inducible or mutational resistance, we recommend a **macrolide-containing** regimen

strong recommendation, very low certainty in estimates of effect

With inducible or mutational macrolide resistance, we suggest a **macrolide** if used as an **immunomodulator**. It is not counted as an active drug

We suggest a multidrug regimen that includes at least **3 active drugs in the initial phase** (guided by in vitro susceptibility)

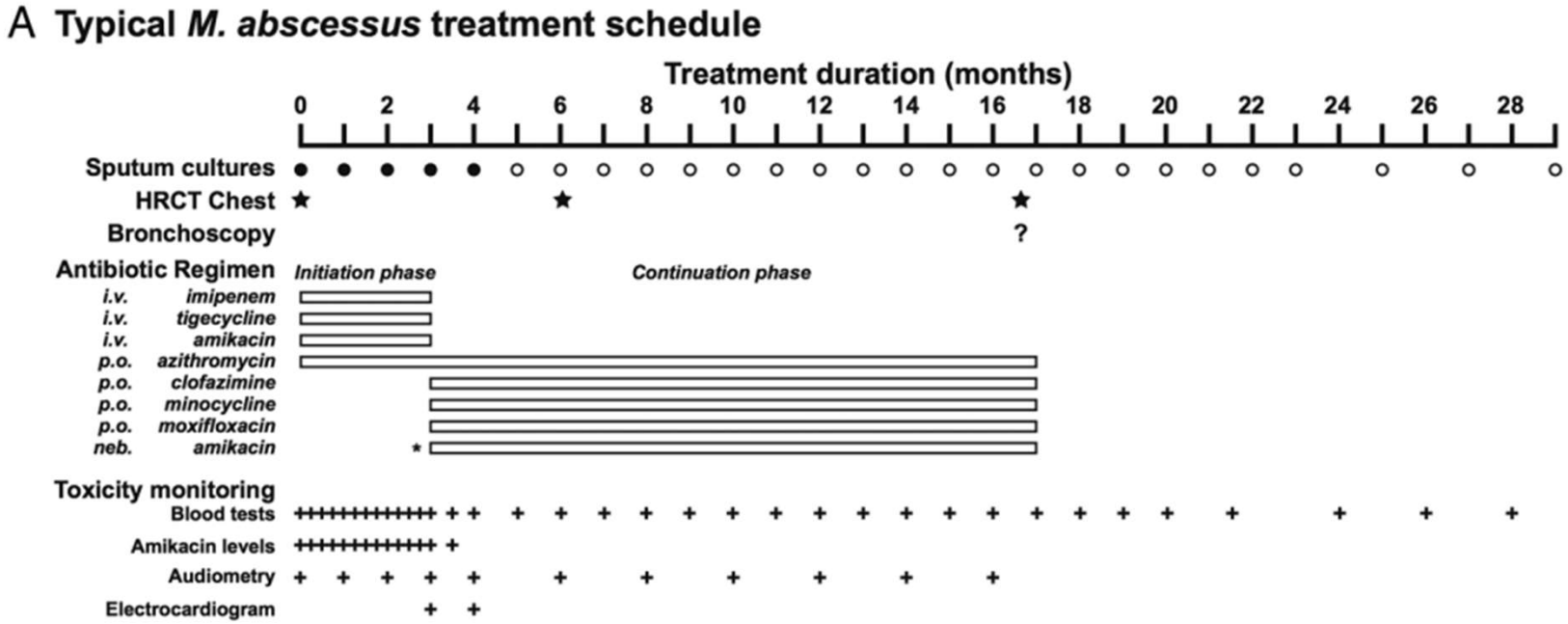
We suggest that either a **shorter or longer** treatment regimen be used and expert consultation obtained

conditional recommendation, very low certainty in estimates of effect

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

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

Floto A et al. Thorax. , 2016, Vol.71 Suppl 1(Suppl 1), p.i1-22



Treatment outcomes of *M. abscessus*: systematic review

- Pasipanodya JG, et al. Antimicrob Agents Chemother 2017; Oct 24;61(11).

Treatment Naive

Species	N	Sustained culture conversion	Sustained culture conversion without relapse	Recurrence rate
M. abscessus	233	77/233 (34%)	52/223 (23%)	40%
M. massiliense	141	117/141 (83%)	118/141 (84%)	7%

Case

67 -year-old female

Caucasian, living in Florida

Chief Complaint: none

Past Medical History:

Bronchiectasis

Former smoker

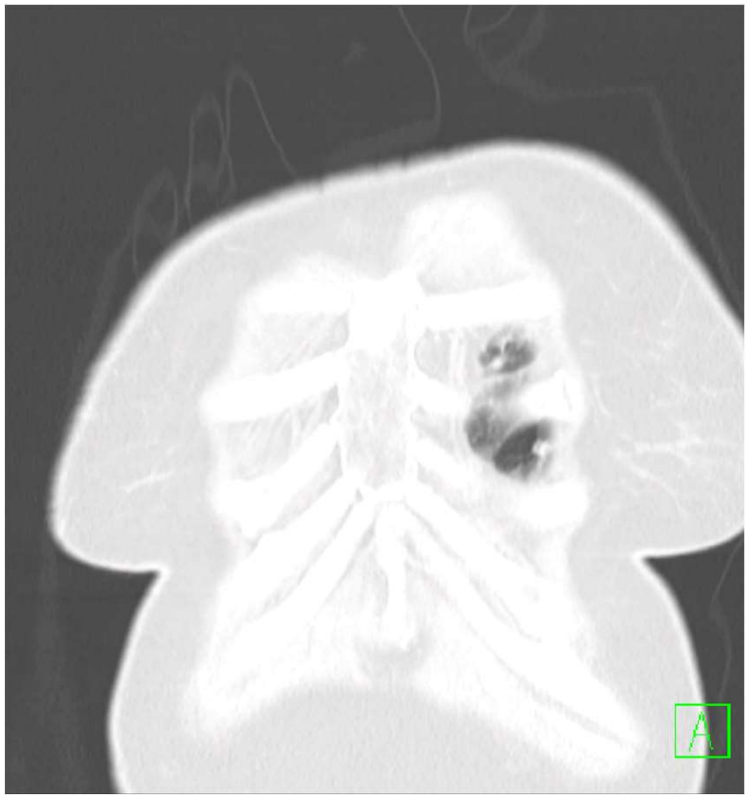
Skin cancer

Medications: none

Cultures: *M. abscessus* subsp *bolletii*

+ inducible macrolide resistance

CT chest 2018



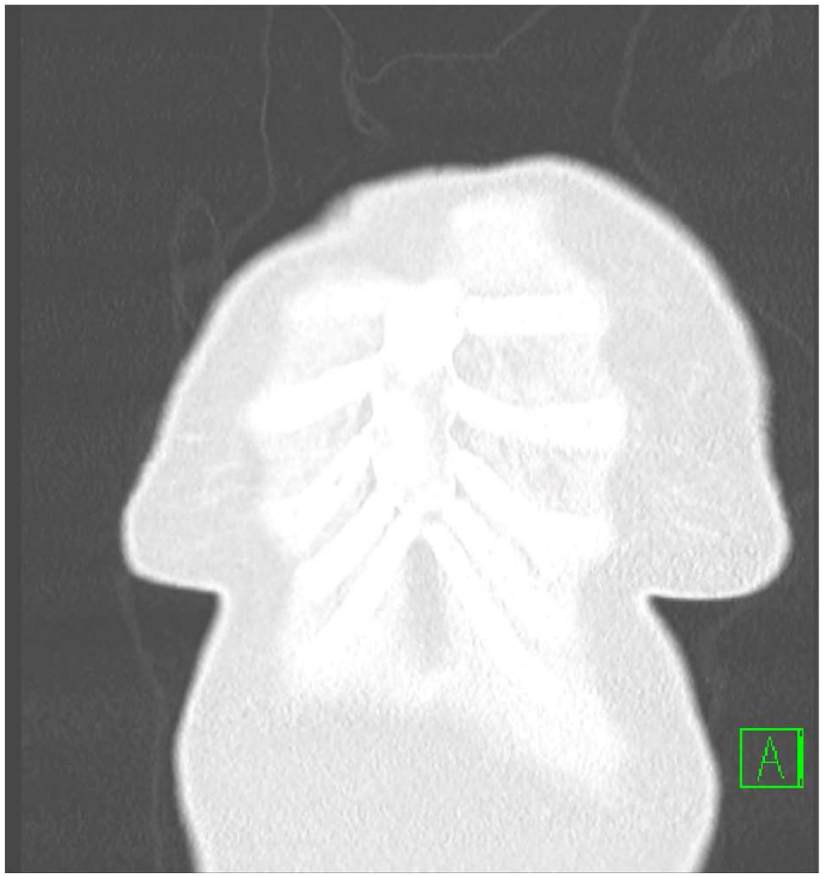
Case

67 -year-old female

	Treatment	Dose	Duration
Initial Rx	Imipenem	1000 mg Q12	2 months
	Amikacin	15mg/kg TIW	2 months
	Tigecycline	50mg Q12	2 months
Cont Rx	Clofazimine	100 mg daily	14 months
	Inhaled amikacin	500 mg TIW	12 months
	Bedaquiline	200 mg TIW	12 months

Treatment ended November 2019 with 12 months of negative cultures

CT chest 2019 post LLLobectomy



Surgical outcomes in *Mycobacterium abscessus*

Indication for surgery	Culture conversion rate	Study design	Reference
Failure of sputum conversion, relapse, hemoptysis	7/8 (88%)	Retrospective observational study	Jeon et al 2009
Focal bronchiectasis cavitation, hemoptysis	15/23 (65%)	Retrospective observational study	Jarand et al 2011
Failure of medical therapy, focal bronchiectasis, cavitation, hemoptysis	16/23 (70%)	Retrospective observational study	Kang et al 2015
Failure of medical therapy, focal bronchiectasis, cavitation, hemoptysis	31/34 (93.9%)	Retrospective observational study	Togo et al 2022

Predictors of favorable outcomes

- BMI >18.5
- Use of azithromycin
- Macrolide susceptible
- *M. massiliense* infection

Park J et al. Clin Infect Dis 2017

- Smooth morphotype

Hedin W et al. Jour Infect Dis 2023

- Lower CT lesion score
- Lower cavity score (MAB)

Park J et al. Respiratory Medicine 2021

- Use of azithromycin, imipenem or amikacin (MAB)

Kwak N et al. Eur Respir J 2019

Weight restoration is KEY

- Park J et al. CID 2017;64(3):301-8
- Jhun BW et al. Eur Respir J 2020; 55: 1900798.

BMI <18.5 kg/m^2	OR	CI	p value
Predictor of progression	4.79	(1.39–16.48)	0.013
Negative Predictor of sustained culture conversion	0.08	(.01–.69)	0.021
Predictor of mortality	3.85	(3.05–4.86)	<0.001

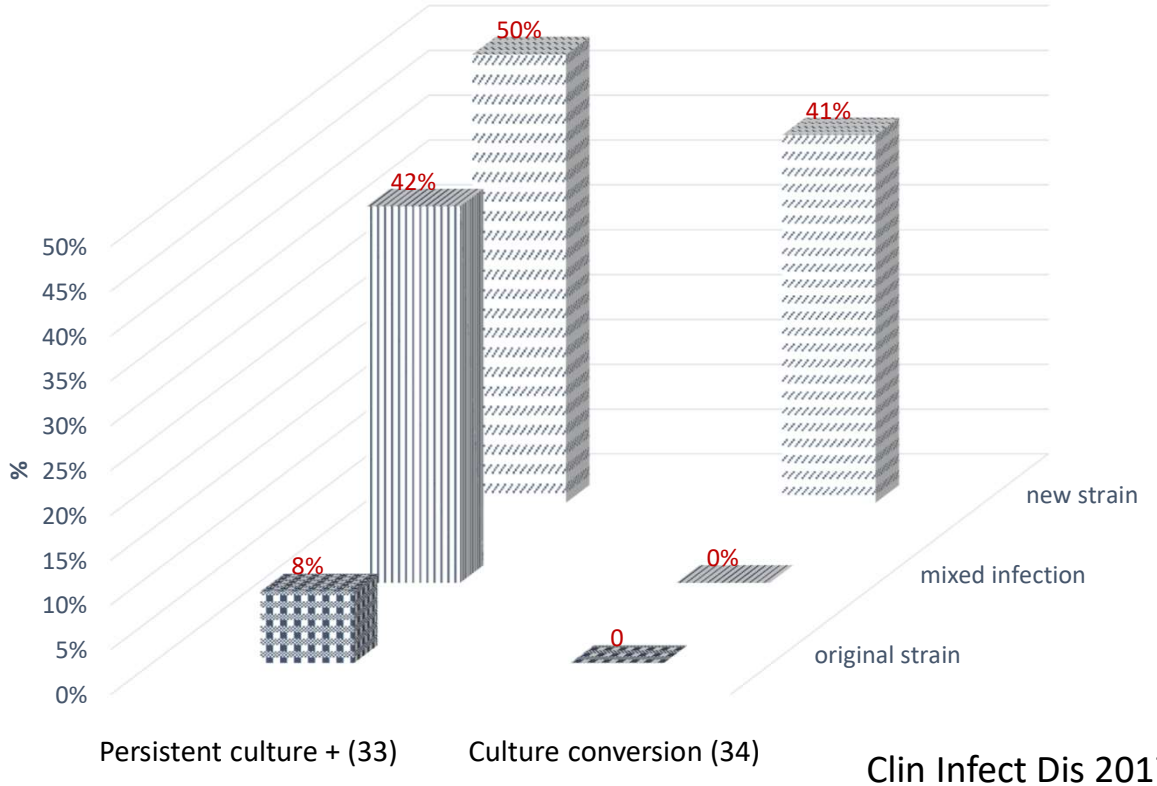
Mortality in *M. abscessus* pulmonary disease

- Jhun BW et al. Eur Respir J 2020; 55: 1900798

All Cause Mortality	5 year	10 year	15 year
M. massiliense	7.3%	18.1%	23.5%
M. abscessus	11.4%	29.8%	50.6%

Relapse vs. Re-infection

Samsung Medical Center (2002-2012)

- 

Clin Infect Dis 2017;64:309-16.

Emerging therapies for *M. abscessus*

Agent	In vitro	In vivo	Clinical experience	Reference
Clofazimine	Synergy with CLR, TIG, AMK, BDQ	Activity in mouse model	Retrospective study (n=42)	Ruth M et al. J. Antimicrob. Chemother. 2019 Van Ingen J et al. Antimicrob. Agents Chemother. 2012 Obregón-Henao, A et al. Antimicrob. Agents Chemother. 2015 Yang et al. Antimicrob. Agents Chemother. 2017,
Bla_{Mab} inhibitors	Activity in reference and clinical isolates	Activity in zebrafish models	Case report of Skin/ST infection	Meir M et al. Antimicrob. Resist. Infect. Control 2018 Kaushik A et al. Antimicrob. Agents Chemother. 2019 Le Run E et al. Antimicrob. Agents Chemother. 2019
Dual beta lactams	Synergy in reference and clinical isolates	Synergy in mouse model	Case report, pulmonary MMA with macrolide resistance	Dousa KM et al. Antimicrob. Agents Chemother 2020 Story-Roller E er al. Antimicrob. Agents Chemother. 2019 Alahmdi et al. Open Forum Infect Dis. 2023
Bedaquiline	Activity in clinical isolates Bactericidal activity with rifabutin	Activity in mouse + zebrafish model	Retrospective study in 10 patients, tolerated	Dupont C et al. Antimicrob. Agents Chemother. 2017 Lee J et al. Antimicrob Agents Chemother. 2021 Philley J et al. Chest 2015

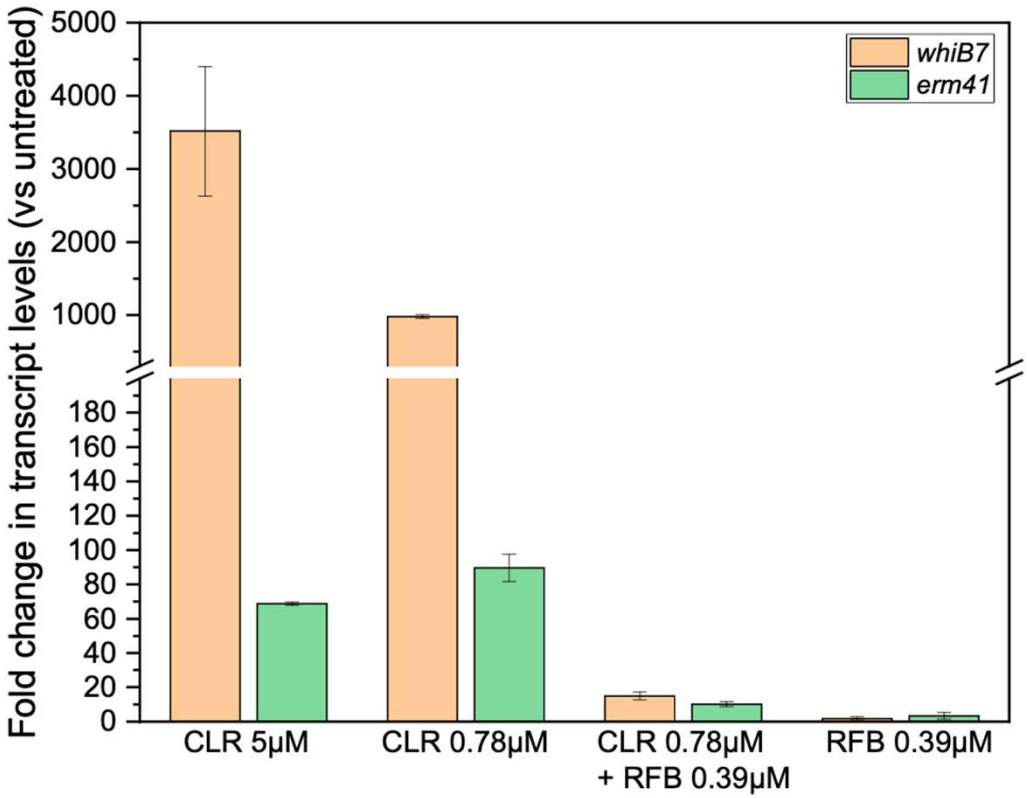
CLR clarithromycin, TIG tigecycline, AMK amikacin, BDQ bedaquiline, MMA Mycobacterium massiliense, ALIS amikacin liposome inhalation suspension

Emerging therapies for *M. abscessus*

Agent	In vitro	In vivo	Clinical experience	Reference
Rifabutin	Activity in clinical CLR R strains, synergy with CLR, suppresses CLR induced resistance	Activity in macrophage, mouse and zebrafish model	Case report in Skin/ST infection	Aziz DB et al. Antimicrob. Agents Chemother. 2017 Ramis IB et al. Med. Chem. 2018 Aziz DB et al. Antibiot 2020 Johansen MD et al. Antimicrob. Agents Chemother. 2020 Dick T et al. Antimicrob. Agents Chemother. 2020
Tedizolid	Activity alone and in combination with CLR, AMK	Activity in macrophage model	Case report Case series SOT (n=15)	Tang YW et al. Front. Microbiol. 2018 Compain F et al. Diagn. Microbiol. Infect. Dis. 2018 Seki M et al. Am. J. Case Rep. 2020. Poon et al. Open Forum Infect Dis. 2021
ALIS	Activity in reference strains, penetrates biofilm	Activity in macrophage model	Retrospective report (n=26) Retrospective report (n=26) Open label study (n=30)	Rose S et al. PLoS One 2014 Le Moigne V et al. J Antimicrob Chemother. 2022 Henriette Zweijpfenning SM et al. Chest 2022 Chiron R et al. Open Forum Infect Dis 2022 Siegel S et al. Chest. 2023
Omadacycline	Activity in sensitive and resistant clinical strains	Activity in mouse pulmonary infection model, HF model	One prospective case report Case series (n=4) Case series (n=5) Case series (n=75)	Nicklas D et al. Antimicrob Agents Chmother 2022 Singh S et al. Int J Antimicrob Agents 2023 Pearson JC et al. Open Forum Infect Dis 2020 Siddiqa S et al. ID Cases 2023 Ghali A et al. Antimicrob Agents Chemother. 2023

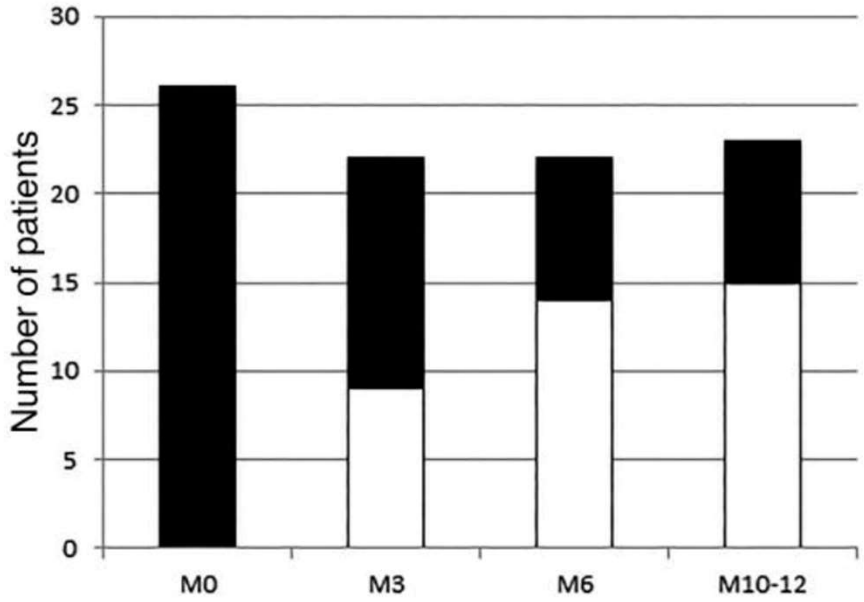
CLR clarithromycin, TIG tigecycline, AMK amikacin, BDQ bedaquiline, MMA Mycobacterium massiliense, ALIS amikacin liposome inhalation suspension

Clarithromycin + Rifabutin decreases transcription of ERM 41



Aziz et al. *Antibiotics* **2020**, *9*, 72; doi:10.3390

Amikacin liposome inhalation suspension (ALIS) in refractory *M. abscessus*



N=26
54% sustained culture conversion
34% when surgery was excluded

Chiron R et al. Open Forum Infect Dis. 2022 Sep 11;9(10)

Dual beta lactam synergy

TABLE 3 MICs of meropenem + vaborbactam + ceftaroline against clinical MAB isolates (mg/L)[a]

Strain	Meropenem	Meropenem + vaborbactam	Imipenem	Imipenem + vaborbactam	Cefoxitin	Cefoxitin + vaborbactam	Ceftaroline	Ceftaroline + vaborbactam	Meropenem + vaborbactam + ceftaroline
MAB027	32	8	8	4	16	16	64	4	1
MAB055	8	8	4	2	16	16	64	4	4
MAB063	16	8	4	4	16	16	64	2	2
MAB066	8	8	8	8	16	8	32	2	2
MAB068	32	16	8	8	32	32	64	4	4
MAB069	32	16	8	4	32	32	32	4	1
MAB077	32	16	32	8	16	16	32	8	8
MAB079	32	8	16	8	32	16	64	8	1

[a]For combination MIC testing, the concentrations of vaborbactam and ceftaroline were fixed at 8 and 1 µg/mL, respectively.

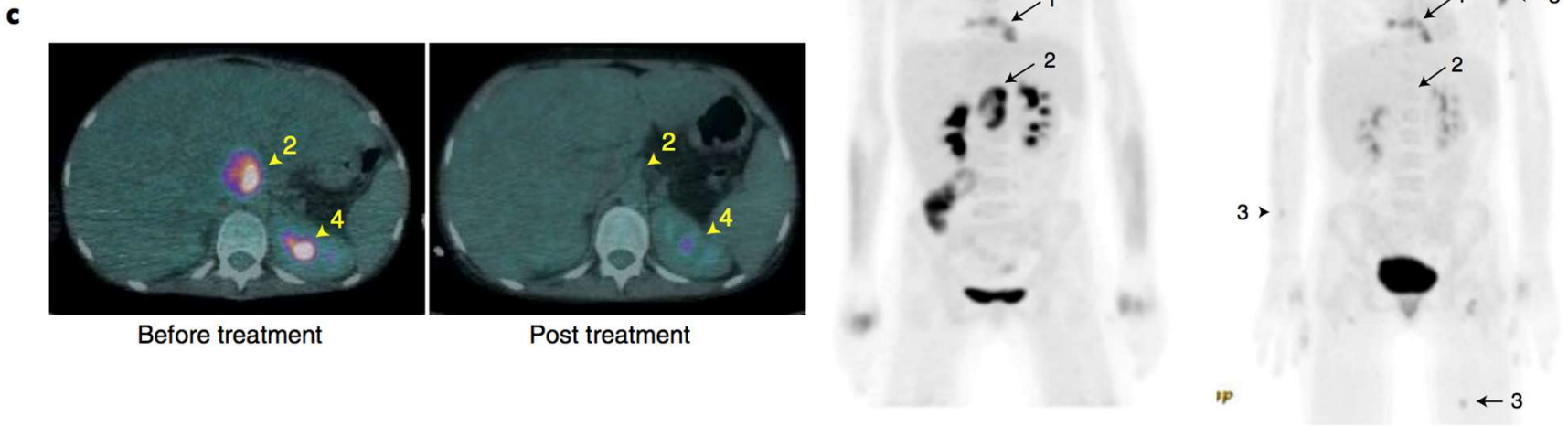
Key point:

-The addition of meropenem + vaborbactam +ceftaroline had the greatest effect on MIC

Chen et al. Antimicrob Agents Chemother. 2024 Apr 1:e0017424.

Engineered Phage Therapy

- 15 yo female with disseminated *M. abscessus* post lung transplant
- NTM treatment for 8 years prior to transplant

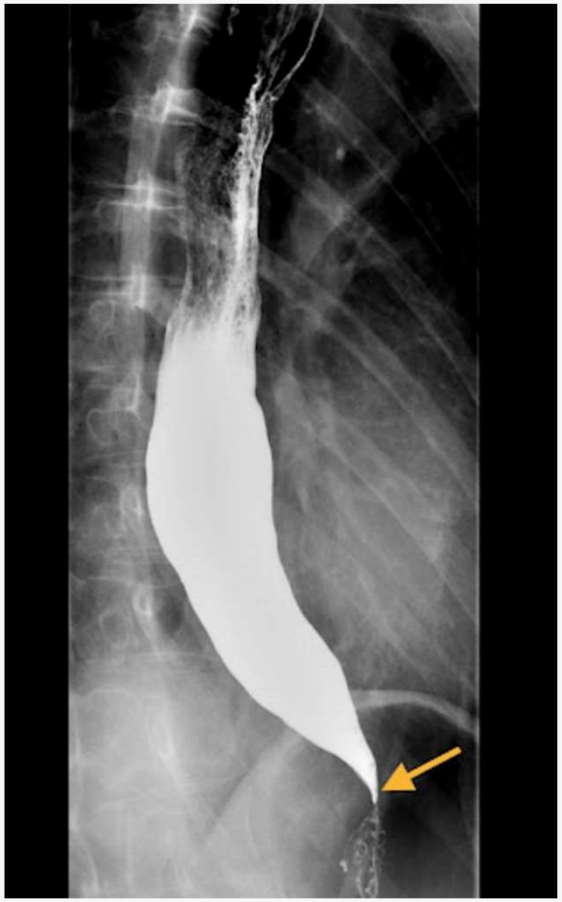


Whole-body (b) and cross-section (c) PET-CT scans 12 weeks before and 6 weeks post phage treatment

Nat Med. 2019 May;25(5):730-733

Mycobacterium fortuitum complex

- *M. fortuitum* complex
  - *M. fortuitum, M. peregrinum, M. porcinum, M. senegalence*
- Typically, sensitive to amikacin (100%), ciprofloxacin (97%), moxifloxacin (97%), imipenem(92%), Trimethoprim sulfamethoxazole (69%), doxycycline (39%), clofazimine
- *M. fortuitum* complex may contain ERM (39) conferring inducible macrolide resistance
- Rare cause of pulmonary disease
- Beware of concomitant aspiration syndromes, GERD



Lange et al. Lancet Infect Dis. 2022 Jul;22(7):e178-e190.

Mycobacterium fortuitum management

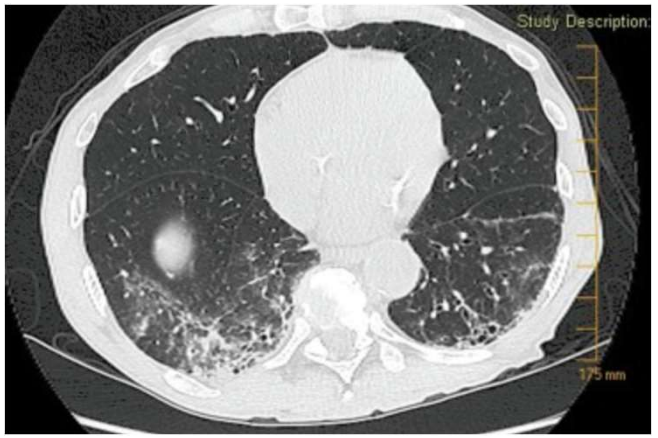
Mycobacterium fortuitum complex	Initially ≥2 for mild to moderate; ≥3 for extensive disease	Parenteral (choose 1-2) **Amikacin** **Imipenem** (or cefoxitin) Tigecycline		Oral (choose 1-2) **Azithromycin*** Moxifloxacin Clofazimine Linezolid TMP/SMX Doxycycline
	Continuation Phase ≥ 2	Oral Azithromycin* Linezolid.	Moxifloxacin TMP/SMX	Clofazimine Doxycycline

- Do NOT use azithromycin if inducible macrolide resistance present
- TMP/SMX trimethoprim sulfamethoxazole
- Treat for 12 months of negative cultures

Lange et al. Lancet Infect Dis. 2022 Jul;22(7):e178-e190.

Mycobacterium chelonae

- Unusual cause of pulmonary disease
- Isolates are usually susceptible to tobramycin (87%), macrolides (96%), clofazimine, linezolid (37%), and sometimes to fluoroquinolones (3%) and imipenem
- Tobramycin is more active in vitro than amikacin
- Generally resistant to cefoxitin
- *M. chelonae* does NOT contain an erythromycin resistance methylase (erm) gene



Lange et al. Lancet Infect Dis. 2022 Jul;22(7):e178-e190.
Pease C. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021 Feb;22: 100209

Mycobacterium chelonae

Mycobacterium chelonae	Initially ≥2 for mild to moderate; ≥3 for extensive disease	Parenteral (choose 1-2) **Tobramycin** **Imipenem** Tigecycline		Oral (choose 1-2) **Azithromycin** Clofazimine Linezolid Moxifloxacin
	Continuation Phase ≥ 2	Oral/inhaled Azithromycin Linezolid	Clofazimine Moxifloxacin	Inhaled amikacin

Treat for 12 months of negative cultures

Lange et al. Lancet Infect Dis. 2022 Jul;22(7):e178-e190.

Summary

- *M. abscessus* is the most common RGM to cause pulmonary disease
- Not all patients progress requiring treatment
- Predictors for progression include low BMI, bilateral, cavitary pulmonary disease
- Macrolide sensitivity is critical to prognosis
- Treatment includes both IV and oral agents
- Cure rates vary from 23%-88%, may be higher with surgical resection
- *M. fortuitum* and *M. chelonae* are RARE causes of pulmonary disease

Questions?