Mycobacterium abscessus pulmonary disease

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Disclosures

Insmed: speaker, advisory board, investigator

Paratek: speaker, advisory board

AN2: advisory board

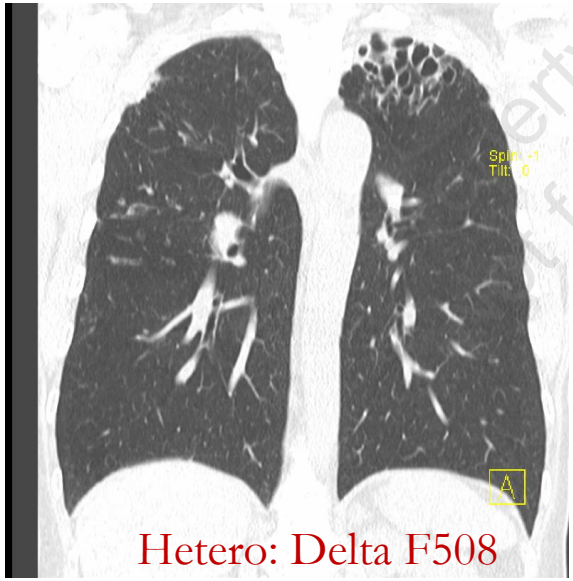
Learning Objectives

- Review the epidemiology
- Examine characteristics of *M. abscessus*
- Illustrate clinical manifestations
- Consider therapeutic options, **challenges** and predictors of outcomes

Cases

- 64 year old female
- Smear -
- Culture *+M. abscessus*
- Diagnosis 2016

Treatment
None



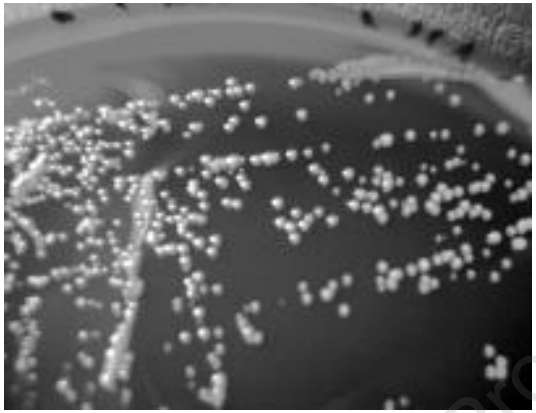
- 64 year old female
- Smear -
- Culture + *M. abscessus*
- Diagnosis 2013

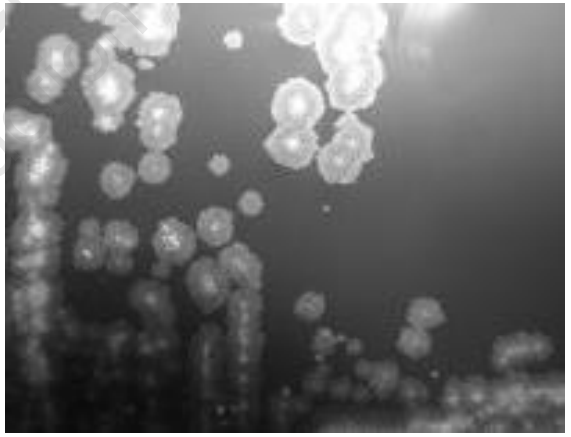
Treatment:
IV/inhaled amikacin
IV tigecycline
IV imipenem
IV imipenem/ceftaz
PO clofazimine
PO linezolid/tedizolid
PO omadacycline
PO bedaquiline
Lobectomy
Phage?

M. abscessus

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

M. abscessus





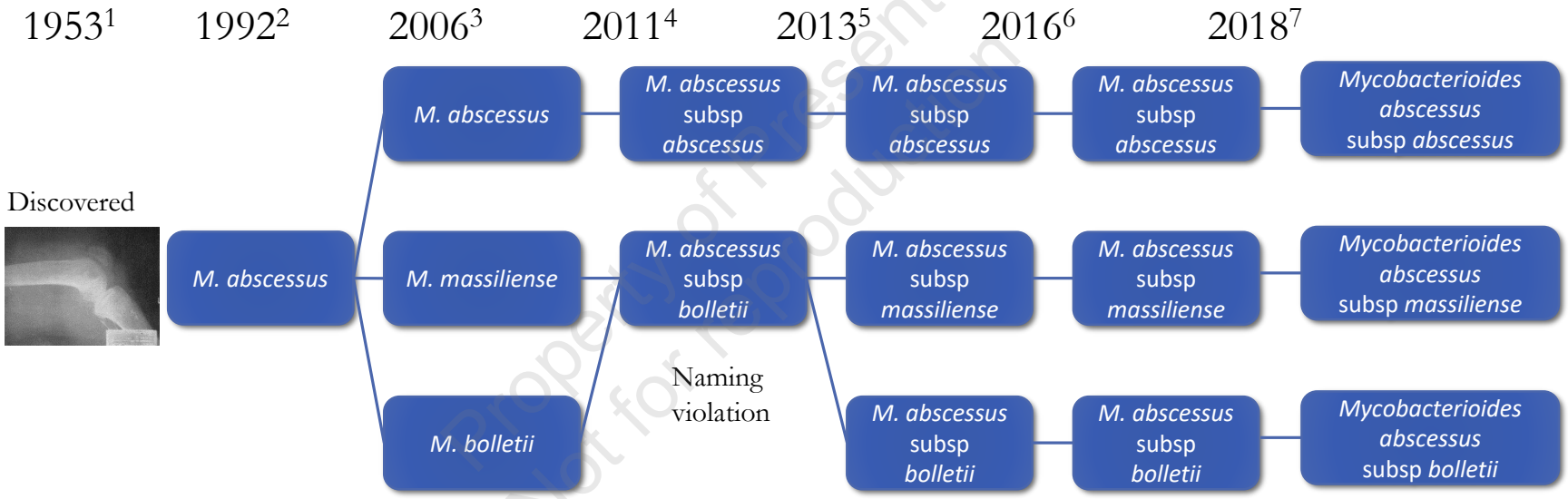
Smooth phenotype

Rough phenotype

J Clin Microbiol 2007;45;1497-1504.

Mycobacterium abscessus

An Evolving Taxonomy

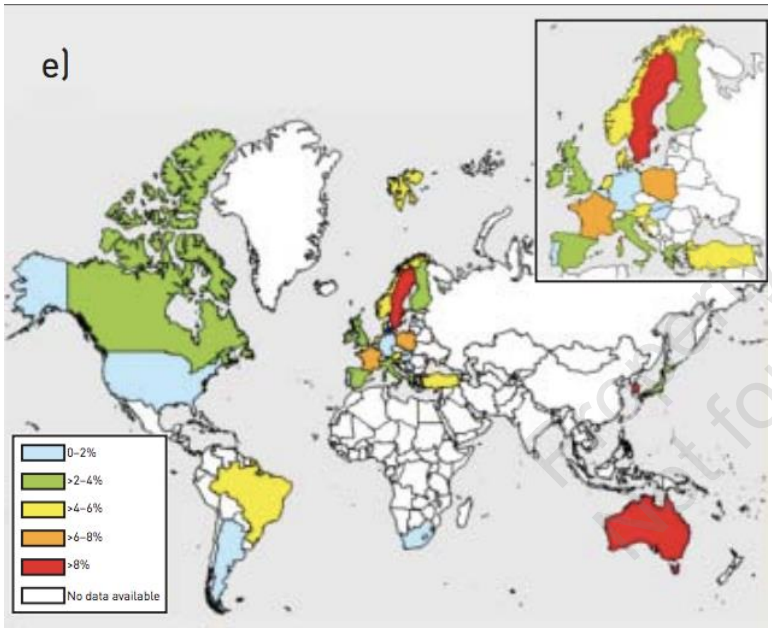


[1]Moore M J Invest Derm 1953;20:133
[2]Kusunoki S. Int J Syst Bacteriol 1992;42:240
[3]Adekambi T. Int J Syst Bacteriol 2006;56:133
[3]Adekambi T. Int J Syst Bacteriol 2006;56:2025
[4]Leao SC. Int J Syst Evol Microbiol 2011;61:2311
[5]Cho YJ. PLoS ONE 2013 8(11):e81560
[6]Tortoli E. Int J Syst Evol Microbiol 2016;66:4471
[7]Gupta RS, et al. Frontiers Microbiol 2018;9:Art 67

Phylogenomics and Comparative Genomic Study

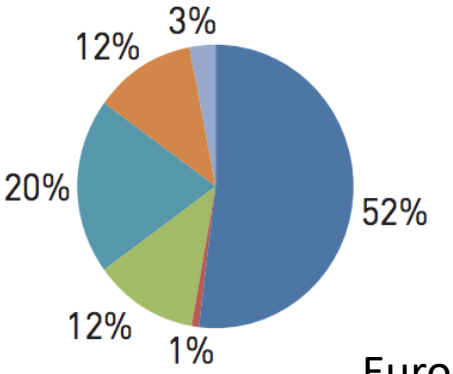
Gupta RS, et al. Front Microbiol. 2018 Feb 13;9:67.

Geographic distribution of NTM isolates: 2008

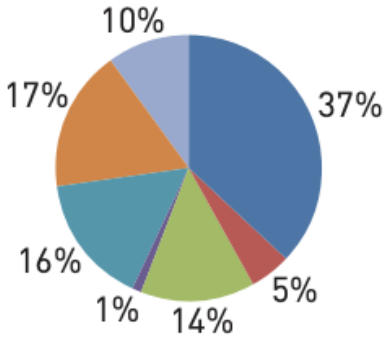


Distribution of NTM
- MAC
- *M. kansasii*
- *M. xenopi*
- *M. malmoense*
- RGM
- *M. gordonae*
- other SGM

N. America



Europe



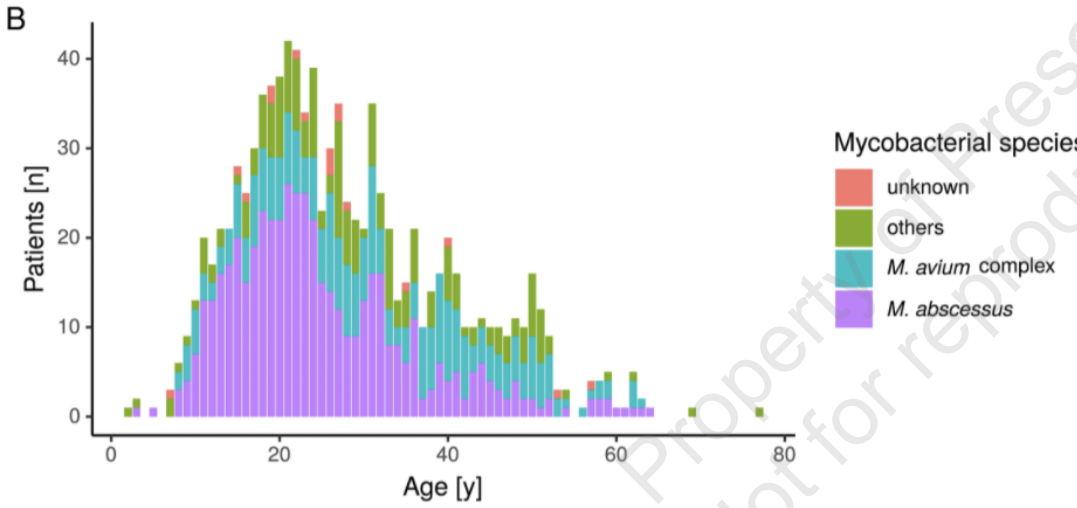
Eur Respir J. 2013 Dec;42(6):1604-13.

Distribution of *M. abscessus* subspecies recovery

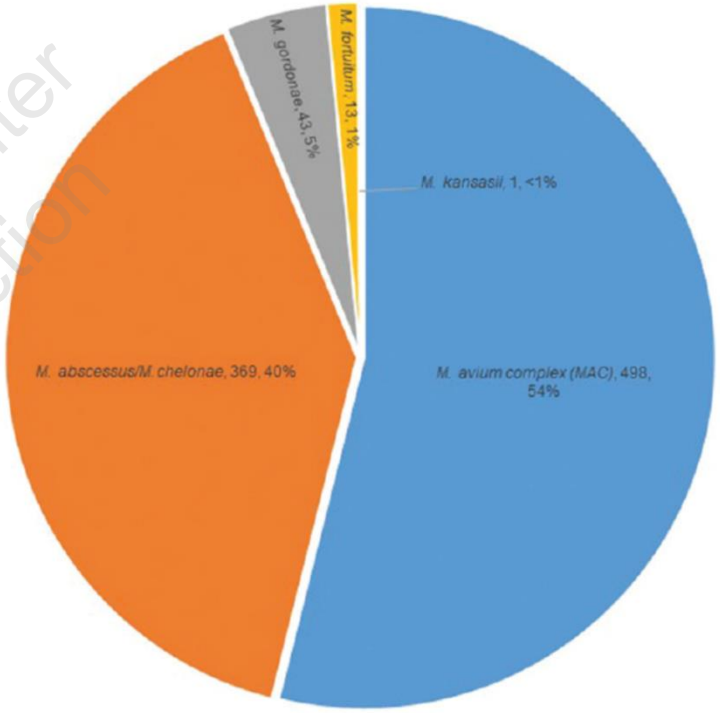
Author (yr)	Country	No.	*Subspecies abscessus*	*Subspecies massiliense*	*Subspecies bolletii*
Zelazny (2009)	USA	40	67.5%	27.5%	5%
van Ingen (2009)	Netherlands	39	64%	21%	15%
Roux (2009)	France	50	60%	22%	18%
Harada (2012)	Japan	102	71%	26%	3%
Yoshida (2013)	Japan	143	63%	35%	2%
Nakanaga (2014)	Japan	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%

Int J Tuberc Lung Dis 2014;18:1141

Distribution of *M. abscessus* in CF cohort (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

M. abscessus and Macrolide resistance

MAB subspecies	CLR susceptibility days 3–5	CLR susceptibility day 14	Macrolide susceptibility phenotype	Genetic implication	Macrolide Effect
massiliense (abscessus)*	Susceptible	Susceptible	Macrolide susceptible	dysfunctional *erm*(41) gene	Anti-mycobacterial
abscessus bolletii	Susceptible	Resistant	Inducible macrolide resistance	functional *erm*(41) gene	Immuno-modulatory
Any	Resistant	Resistant	High-level constitutive macrolide resistance	23S ribosomal RNA point mutation	Immuno-modulatory

*15-20% of *subspecies abscessus* have a dysfunctional ERM41 (C28)

CLR: Clarithromycin

Thorax 2017;72(Suppl 2):ii1

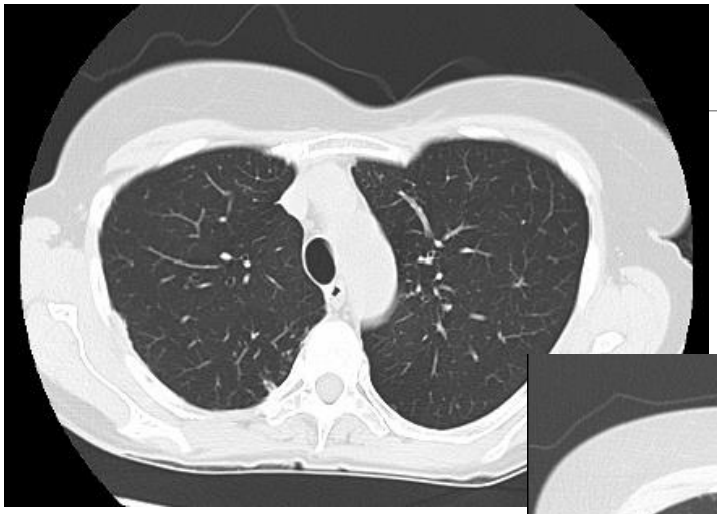
Antibiogram of *M. abscessus*

Organism	n	CLR*	AMK	TOB	CIP	MXF	FOX	IPM	LZD	SXT	DOX
M. abscessus subsp. *abscessus*	1344	61	93	1	0	0	30	19	8	0	0
M. abscessus subsp. *bolletii*	93	61	92	2	0	0	19	15	14	0	0
M. abscessus subsp. *massiliense*	754	95	82	0	1	1	28	12	9	0	0

Diagn Microbiol Infect Dis. 2023 Mar;105(3):115882

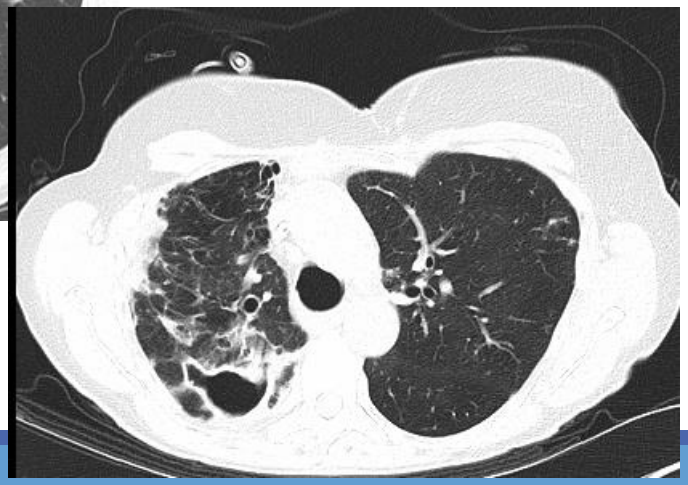
Chronic Pulmonary Disease

2003



2013

2017



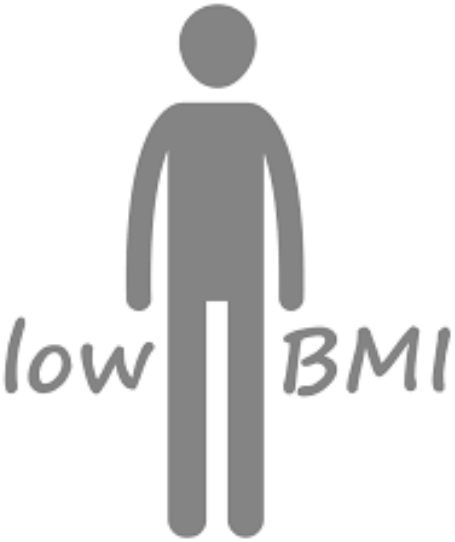
Clinical manifestations

Characteristic	Resistant group (69)	Sensitive group (31)	P value
Age, median (IQR)	58 (44-66)	56 (32-64)	0.562
Males, n (%)	26 (37.7)	17(54.8)	0.107
BMI, mean	19.93	19.69	0.729
Bronchiectasis	66 (95.7)	29 (93.4)	0.655
Cavity	**50 (72.5)**	**8 (25.8)**	**<0.001**
Nodules	38 (55.0)	19 (61.3)	0.648
Tree in bud	**16 (23.2)**	**14 (45.2)**	**0.027**
Cough, n (%)	55 (79.7)	25 (80.6)	0.914
Sputum, n (%)	69 (100.0)	31 (100.0)	1
Fever, n (%)	15 (21.7)	4 (12.9)	0.298
Hemoptysis, n (%)	**22 (31.9)**	**4 (12.9)**	**0.045**

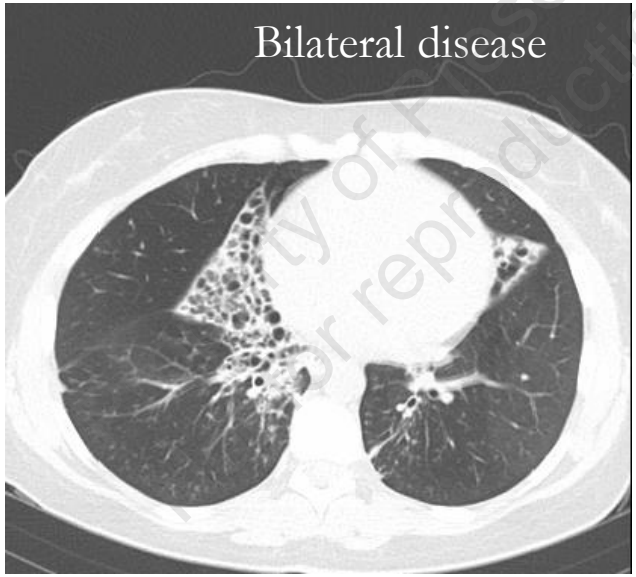
Antimicrob Agents Chemother. 2018 Apr 26;62(5)

Predictors of progression

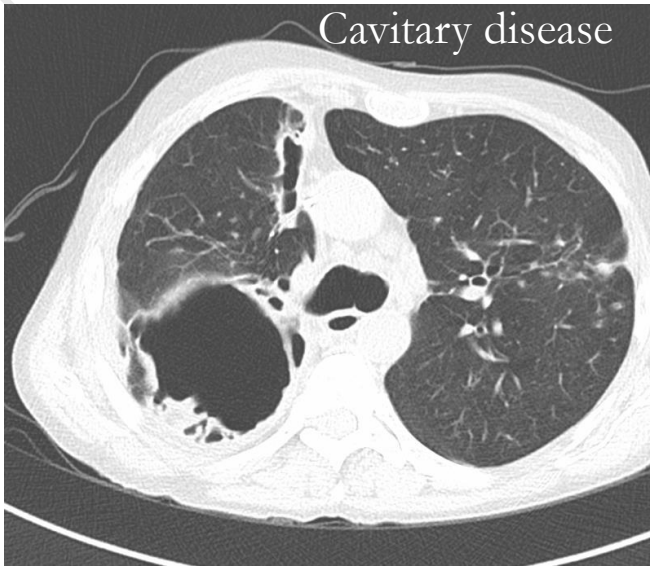
N=113 median follow up 3.4 years, Seoul National University



OR 4.79 (1.39–16.48)
p .013

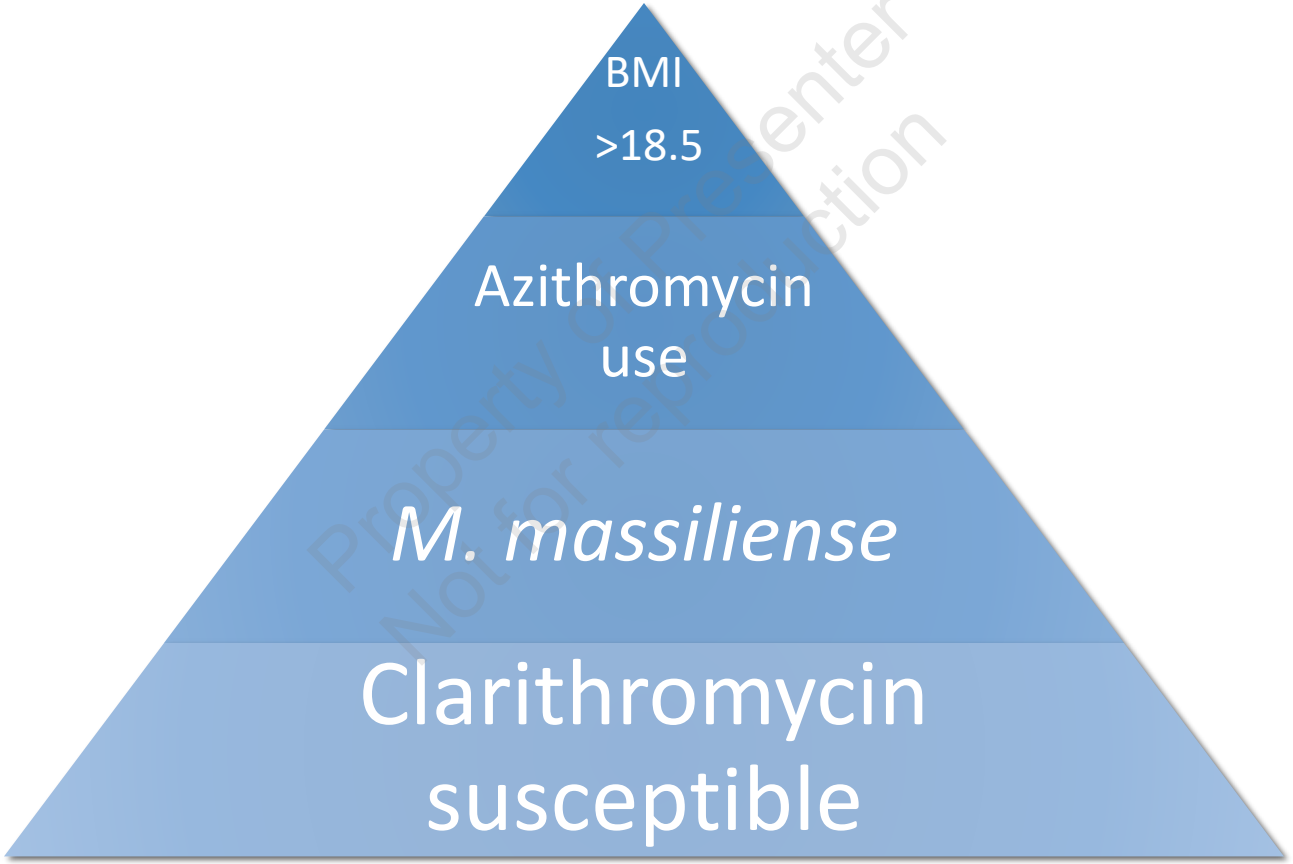


OR 3.83 (1.06–13.82)
p .040



OR 3.62 (1.02–12.82)
p .046

Predictors of favorable outcome



CID 2017;64(3):301–8.

Predictors of favorable outcomes: Mycobacterial characteristics

Mycobacterial characteristics	Negative culture (20)	Persistently positive (24)	P value
Smooth morphotype	9 (45)	2 (8)	.020
Rough morphotype	7 (35)	14 (58)	
CLR Susceptible	7 (35)	1 (4)	.015
Inducible resistance	13 (65)	23 (96)	
C28 sequevar	6 (30)	1(4)	.035
T28 sequevar	14 (70)	23(96)	

CID 2017;64(3):309–16.

Treatment outcomes: Shanghai Hospital

Outcome	Resistant group (69)	Sensitive group (31)	P value
Median duration of treatment, mo IQR	18 (9-30)	15 (9-22)	0.260
Initial conversion	30 (43.5)	22 (71.0)	**0.011**
Median time to initial conversion, mo (IQR)	12 (6-23)	7 (5-11)	**0.004**
Convert to stable negative	21 (30.4)	19 (61.3)	**0.013**
Radiology improved	25 (36.2)	22 (71)	**0.006**
Treatment effective	30 (43.5)	26 (83.9)	**<0.001**

*resistant: inducible or mutational resistance to macrolides

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

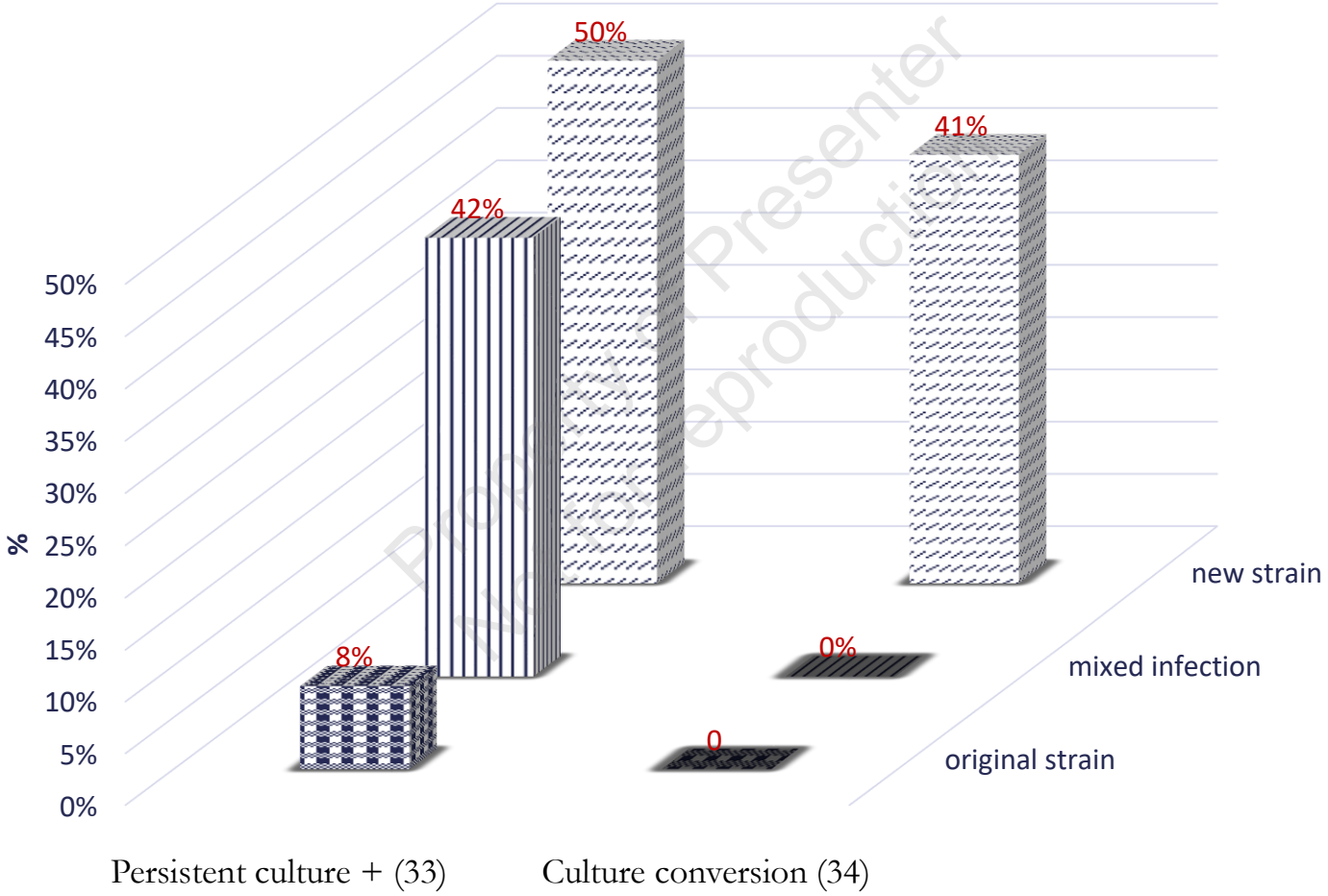
Treatment of M. abscessus: systematic review

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

Antimicrob Agents Chemother 2017; Oct 24;61(11).

Relapse vs. Re-infection

Samsung Medical Center (2002-2012)



Clin Infect Dis 2017;64:309-16.

4 wk vs. 2 wk IV therapy in *M. massiliense*

Treatment outcome data After 12 months of Rx	4week IV group (28)	2 week IV group (43)	P value
Symptomatic improvement	25 (89)	43 (100)	.057
HRCT improvement	22 (79)	39 (91)	.177
Sputum conversion	28 (100)	39 (98)	.148
Conversion at the end of Rx	28 (100)	42 (98)	1.00
Follow up after Rx completion, Mo	33.8 (12.3-50.3)	14.7 (0.5-29.5)	.006
Microbiologic recurrent	2/28 (7)	3/42 (7)	1.00

CHEST 2016; 150(6):1211-1221

Treatment of *M. abscessus*
BTS guidelines

Phenotype	Intensive phase ≥1month*	Continuation phase
CAM sensitive or Inducible resistance	• IV amikacin 15mg/kg daily or 3×per week • IV tigecycline 50mg 2x/d • IV imipenem 1g 2x/d • PO clarithromycin 500mg 2x/d or oral azithromycin 250–500mg daily	• nebulised amikacin • clarithromycin 500mg 2x/d or azithromycin 250–500mg daily • 1–3 of the following • clofazimine 50–100mg daily • oral linezolid 600mg daily or • minocycline 100mg twice daily • oral moxifloxacin 400mg daily • oral cotrimoxazole 960mg 2x/d
Constitutive macrolide resistance	• IV amikacin 15mg/kg daily or 3×per week • IV tigecycline 50mg 2x/d • IV imipenem 1g 2x/d • PO clarithromycin 500mg 2x/d or oral azithromycin 250–500mg daily	• nebulised amikacin • 2-4 of the following • clofazimine 50–100mg daily • oral linezolid 600mg daily or • minocycline 100mg twice daily • oral moxifloxacin 400mg daily • oral cotrimoxazole 960mg 2x/d

Haworth CS et al. *BMJ Open Respir. Res.* **2017**, *4*, e000242.

Treatment of *M. abscessus*
BTS guidelines

Phenotype	Intensive phase ≥1month*	Continuation phase
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Constitutive macrolide resistance	• IV amikacin 15mg/kg daily or 3×per week IV tigecycline 50mg 2x/d • IV imipenem 1g 2x/d • PO clarithromycin 500mg 2x/d or oral azithromycin 250–500mg daily *	• nebulised amikacin • 2-4 of the following • clofazimine 50–100mg daily • oral linezolid 600mg daily or ~~• minocycline 100mg twice daily~~ ~~• oral moxifloxacin 400mg daily~~ ~~• oral cotrimoxazole 960mg 2x/d~~

2020 ATS/ERS/ESCMID/IDSA Guidelines

In patients with *M. abscessus* pulmonary disease, should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

- In patients with *M. abscessus* pulmonary disease caused by strains without inducible or mutational resistance, we recommend a macrolide-containing multidrug treatment regimen
  - strong recommendation, very low certainty in estimates of effect
- In patients with *M. abscessus* pulmonary disease caused by strains with inducible or mutational macrolide resistance, we suggest a macrolide-containing regimen if the drug is being used for its **immunomodulatory** properties although the macrolide is not counted as an active drug in the multidrug regimen
  - conditional recommendation, very low certainty in estimates of effect

Eur Respir J 2020; 56: 2000535

2020 ATS/ERS/ESCMID/IDSA Guidelines

In patients with *M. abscessus* pulmonary disease, how many antibiotics should be included within multidrug regimens?

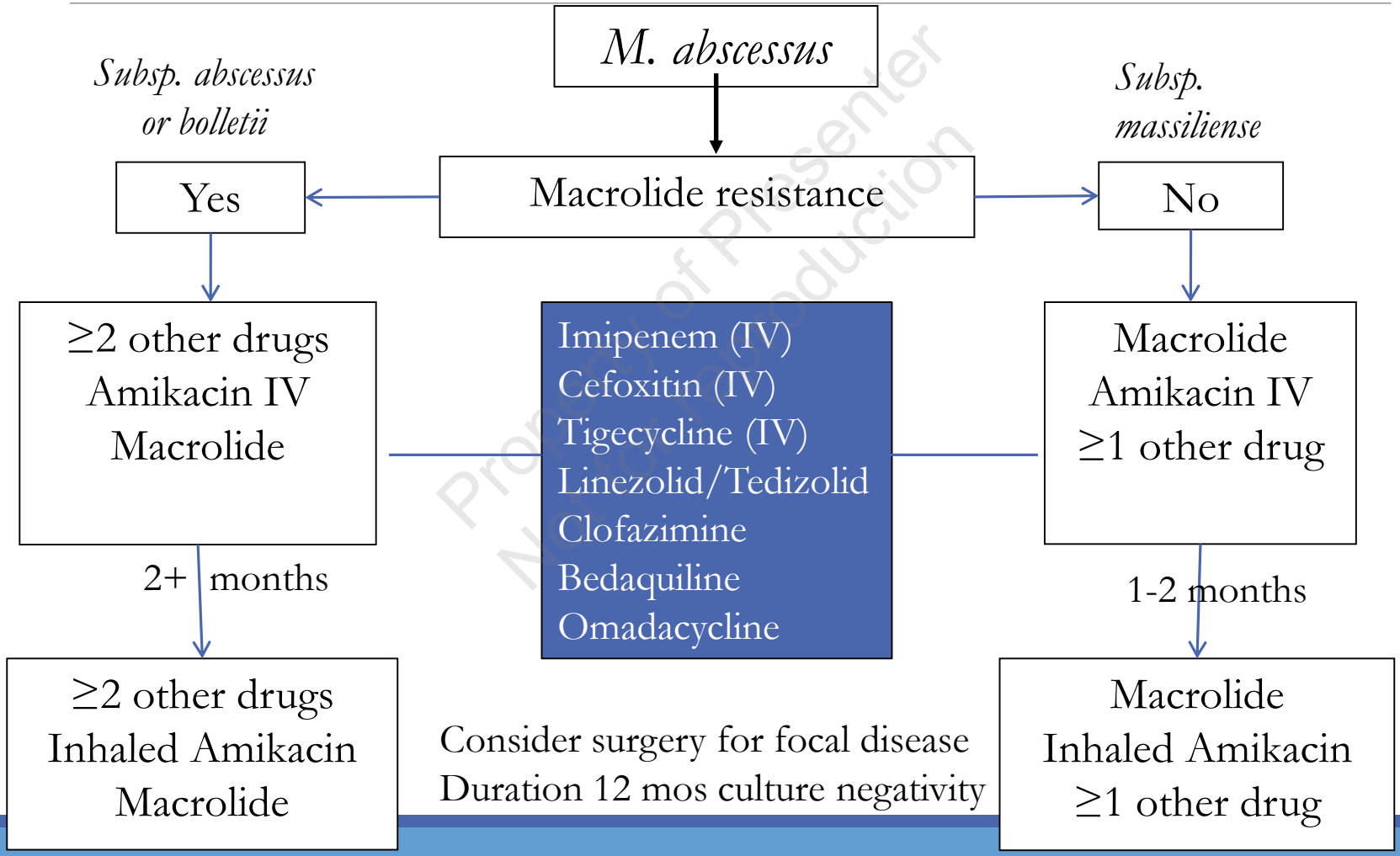
- In patients with *M. abscessus* pulmonary disease, we suggest a multidrug regimen that includes at least 3 active drugs (guided by in vitro susceptibility) in the initial phase of treatment
  - conditional recommendation, very low certainty in estimates of effect

2020 ATS/ERS/ESCMID/IDSA Guidelines

In patients with *M. abscessus* pulmonary disease, should shorter or longer duration therapy be used for treatment?

- In patients with *M. abscessus* pulmonary disease, we suggest that either a shorter or longer treatment regimen be used and expert consultation obtained
  - conditional recommendation for either the intervention or the comparison, very low certainty in estimates of effect

Treatment of *M. abscessus*

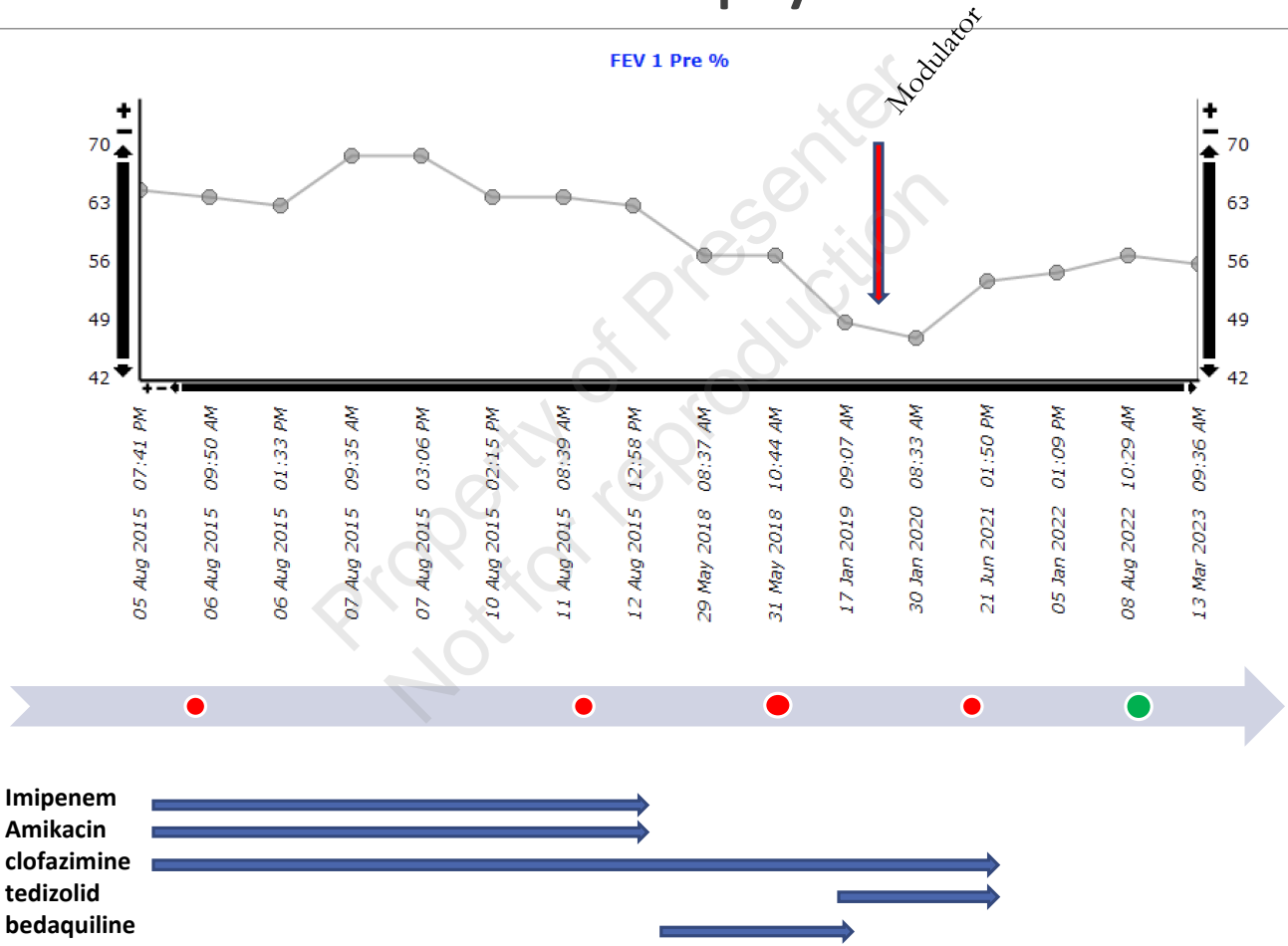


Cases

- 64 year old female
- Smear -
- Culture *+M. abscessus*
- C28, smooth morphotype

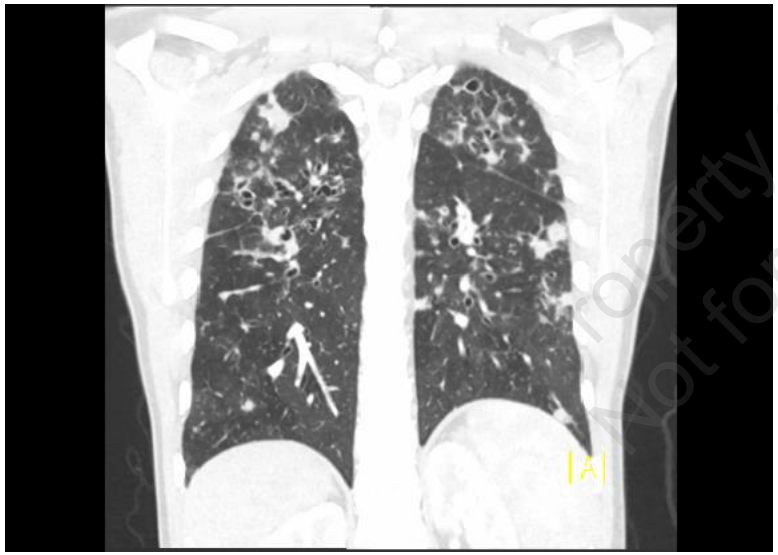
- 64 year old female
- Smear -
- Culture + *M. abscessus*
- T28, rough morphotype

Modulator therapy effect

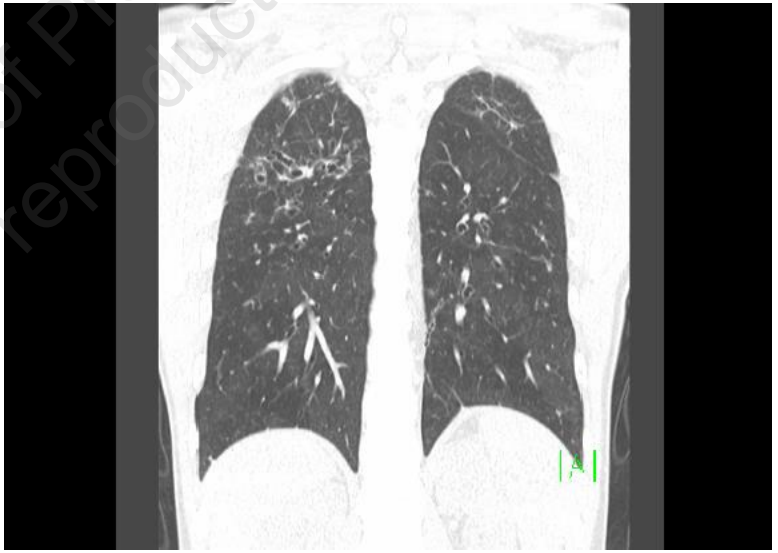


Modulator therapy effect:

9/2018



1/2022- off treatment 12 mo.



Teaching in Thailand

23 year old female

Productive cough for one year

Developed while in Thailand

BAL in Thailand – for TB/NTM/fungi

BAL at NJ: -

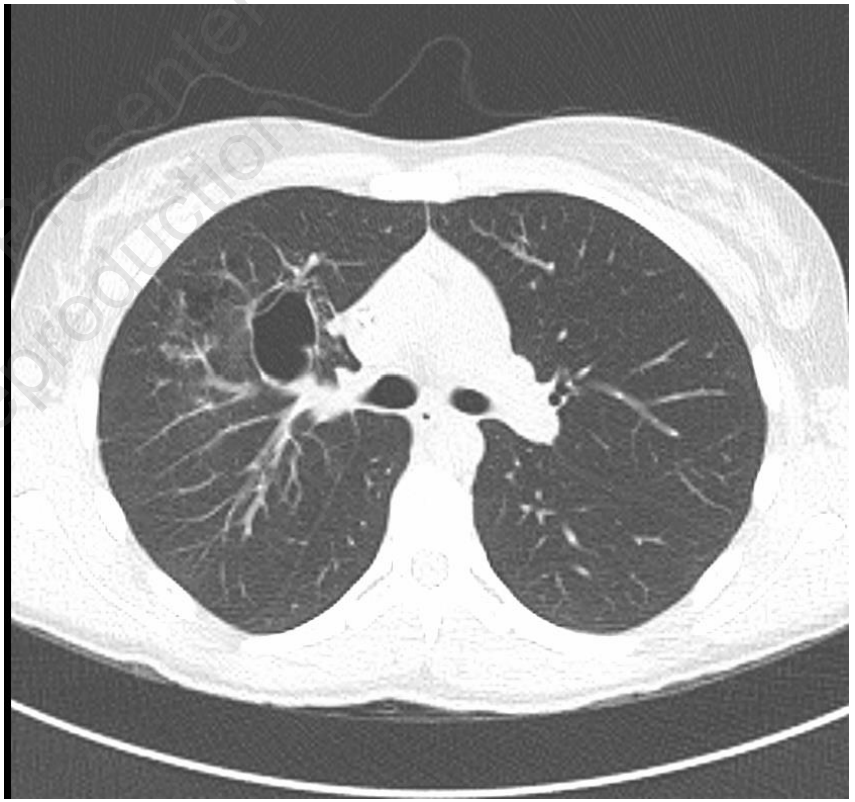
3 induced sputum: + *M. abscessus*

M. abscessus subspecies *abscessus* C28 sequevar

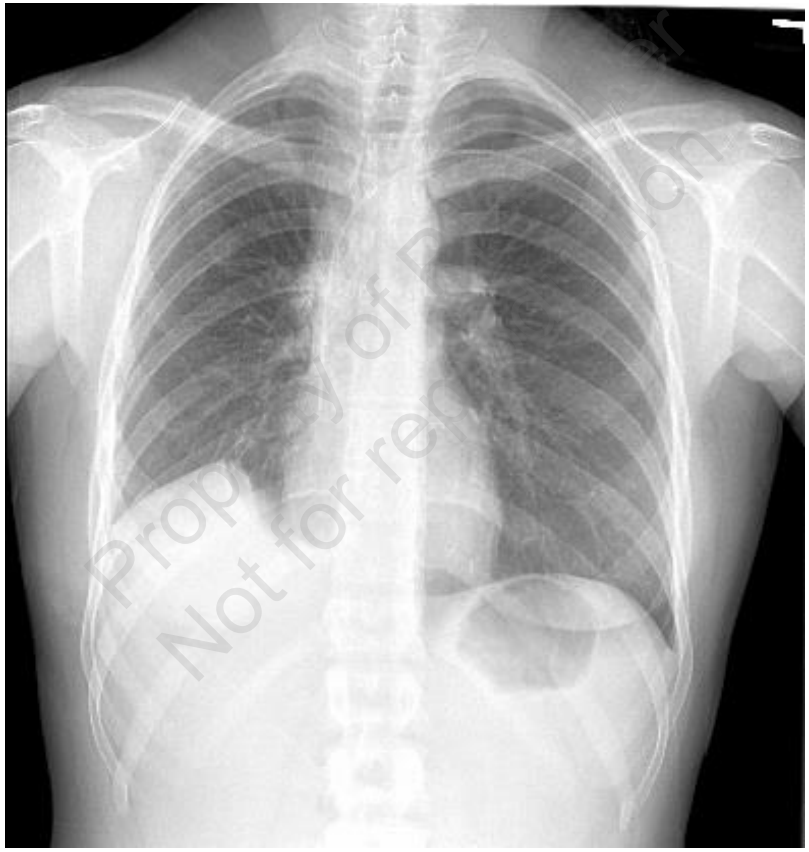
10/2017

1/2018

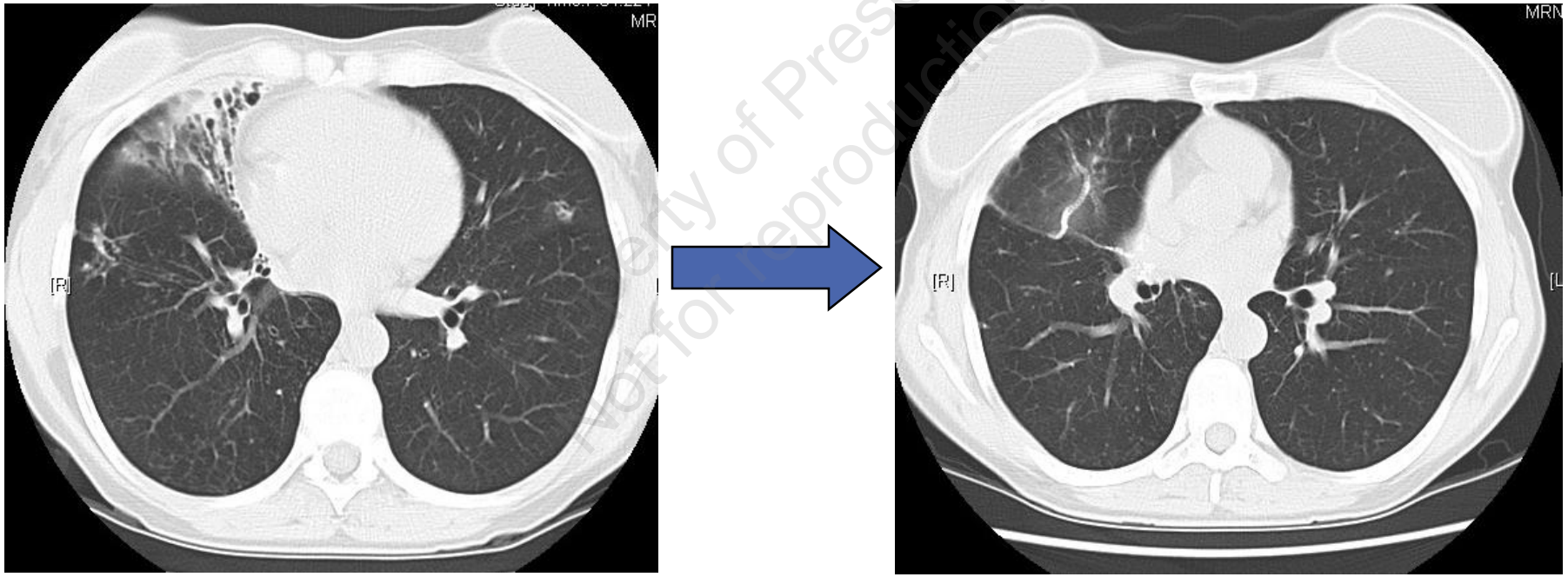
M. abscessus subspecies *abscessus* C28 sequevar



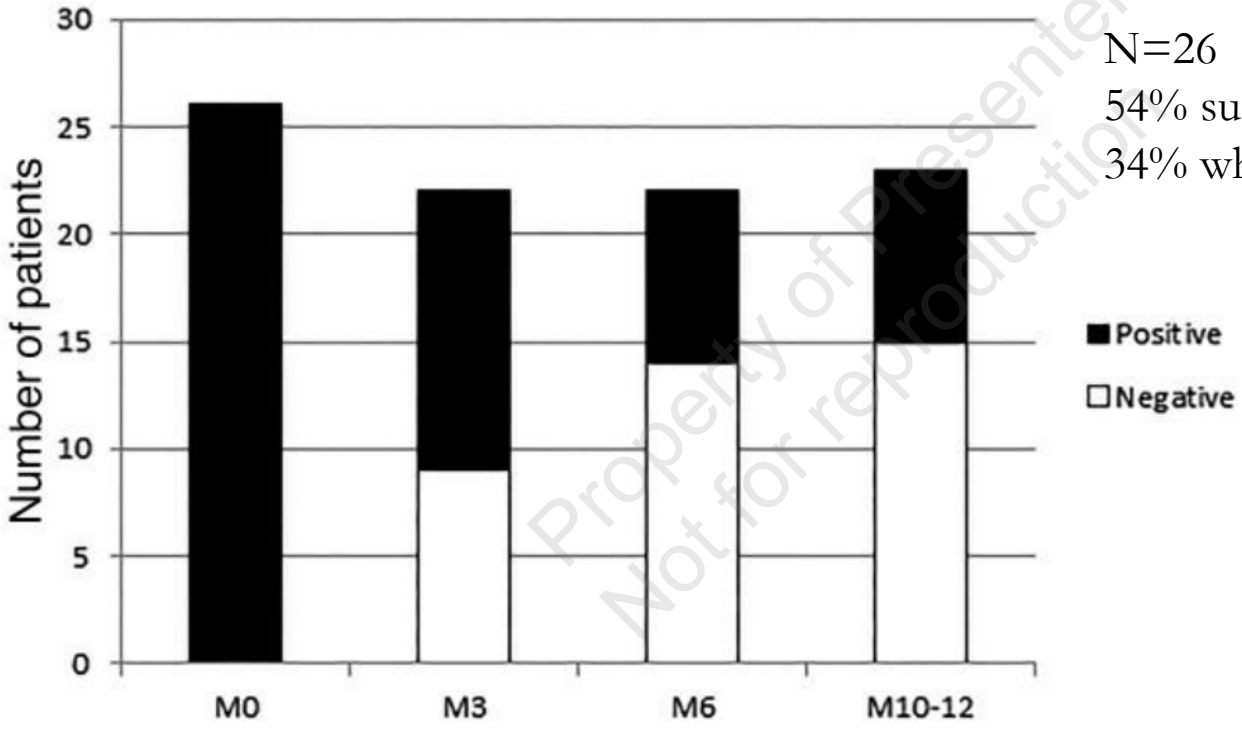
Post right upper lobectomy



Treatment of *M. abscessus:* Surgery



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



N=26

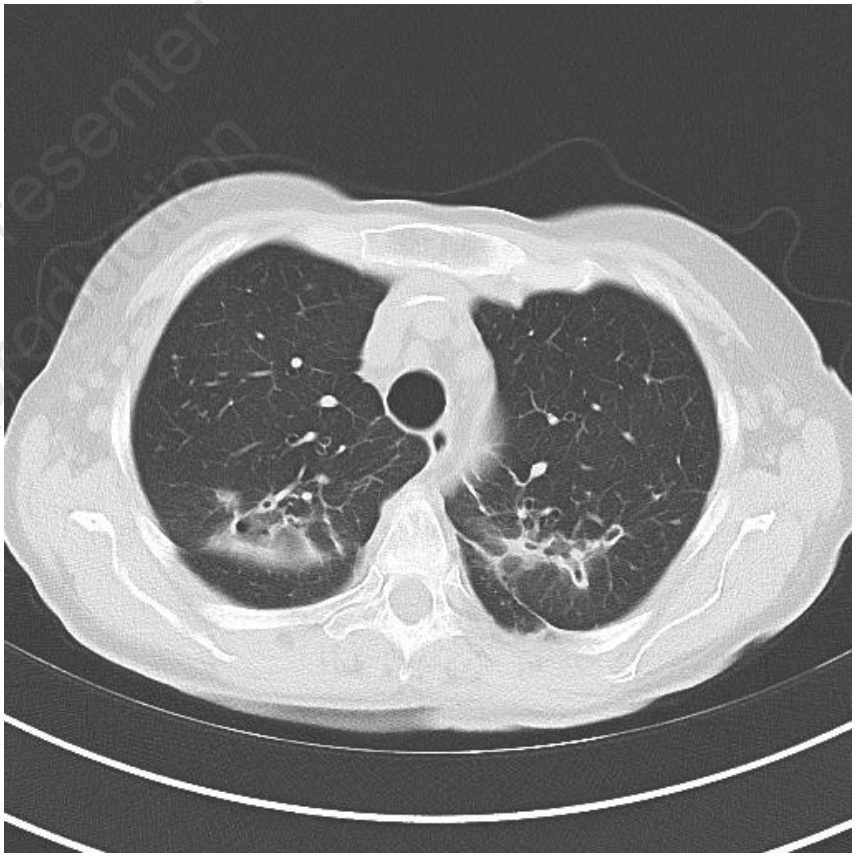
54% sustained culture conversion

34% when surgery was excluded

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

M. abscessus subsp. abscessus T28 sequevar (Dx 2013)
Round 3: IV avibactam/ceftazidime + meropenem + clofaz + linezolid

11/2018



3/2019

Dual beta-lactam synergy

TABLE 2 Activities of ceftaroline or imipenem alone and in combination with increasing concentrations of ceftazidime and/or avibactam against *M. abscessus* complex isolates[a]

Strain	Species	MIC (μg/ml)										
		CAZ + AVI4	CFT	CFT + CAZ10	CFT + CAZ50	CFT + CAZ100	CFT + CAZ100 + AVI4	IMI	IMI + CAZ10	IMI + CAZ50	IMI + CAZ100	IMI + CAZ100 + AVI4
ATCC 19977	*M. abscessus*	512	32	0.25	0.125	0.125	<0.25	8	2	0.25	0.125	0.25
51412	*M. abscessus*	256	8	0.5	0.5	0.5	1	0.5	0.25	0.06	0.06	0.5
51403	*M. abscessus*	128	8	1	0.25	0.125	0.25	8	1	0.5	0.5	0.5

[a]CAZ, ceftazidime; AVI, avibactam; CFT, ceftaroline; IMI, imipenem; CAZ10, 10 μg/ml ceftazidime; CAZ50, 50 μg/ml ceftazidime; CAZ100, 100 μg/ml ceftazidime; AVI4, 4 μg/ml avibactam.

MBio. 2019 Feb 12;10(1)

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

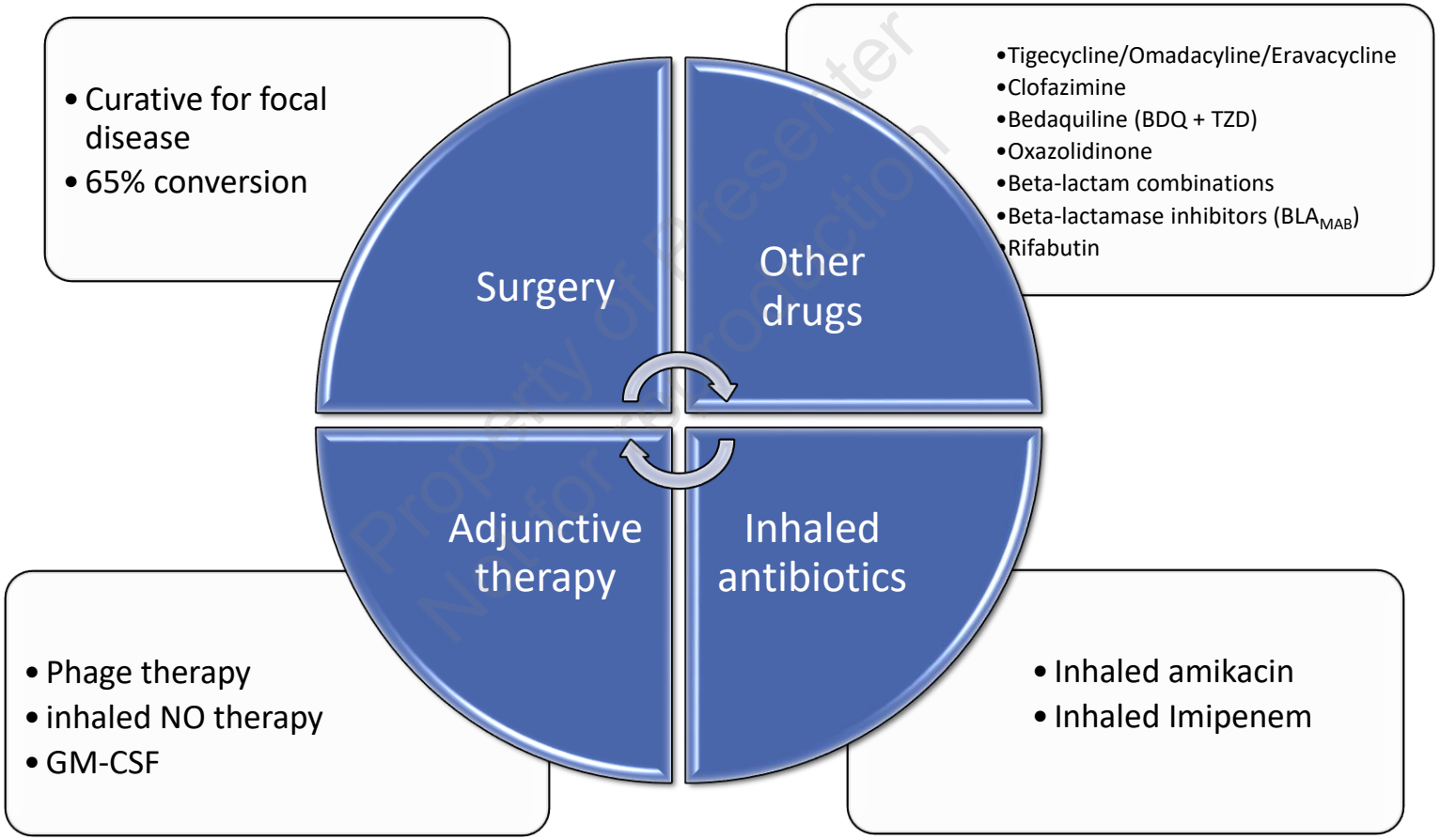
Phage were administered intravenously, through inhalation or both in 20 patients with symptomatic mycobacterial infections

Results:

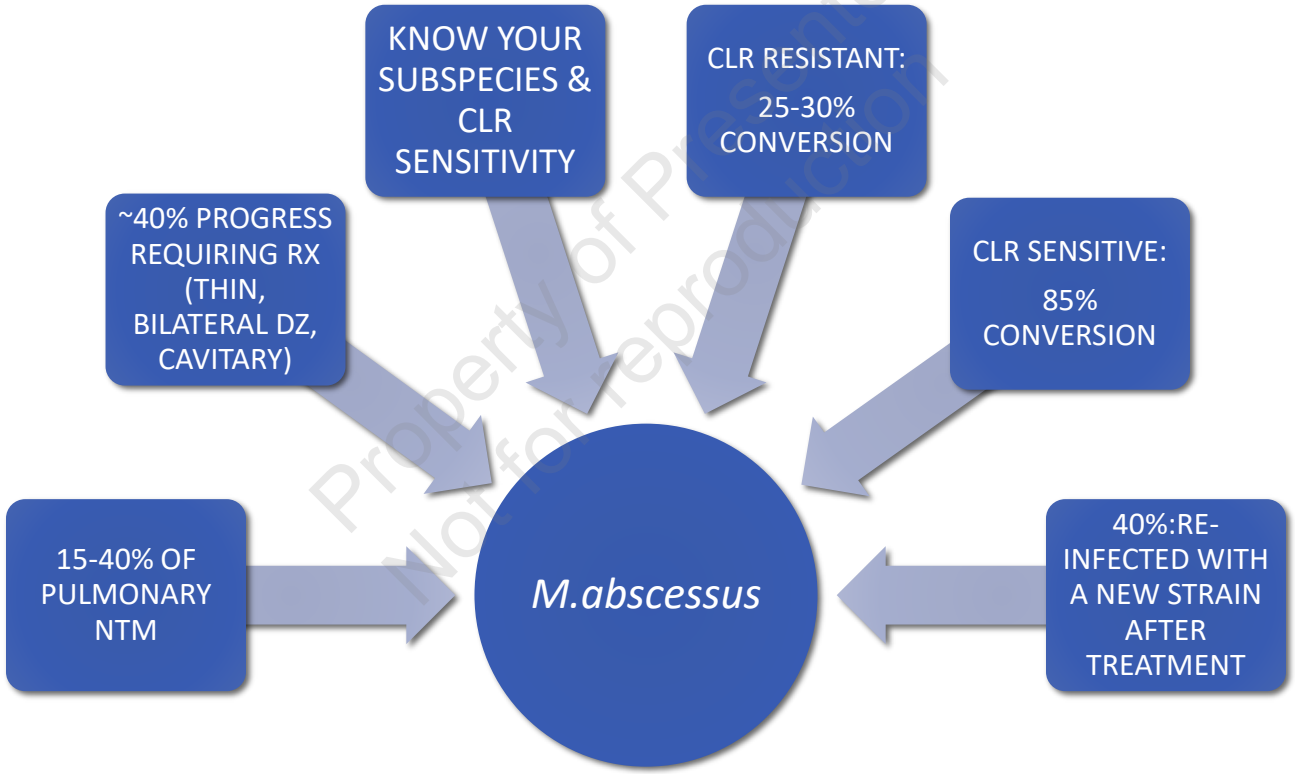
- No adverse reactions occurred
- Favorable clinical or microbiologic responses were seen in 11 patients
- Neutralizing antibody was identified in 8 patients possibly contributing to lack of treatment response
- A single phage was administered in 11 patients and no phage resistance was identified

Dedrick R, et al. CID 2022

Treatment refractory considerations



Summary of Pulmonary *M. abscessus*



Questions?