

La terapia delle micobatteriosi non tubercolari

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Treatment of NTM

- **Very long** treatment (12 months from negative cultures) with significant side effects and poor efficacy rates
 - ATS criteria for infection (vs. colonization)
 - Weight benefits and potential harms
 - Involve patients in the decision
- Very few RCTs to guide treatment
 - Number and choice of drugs depend on the
 - NTM specie
 - Severity of the diseases
 - Concomitant disorders
- **Usually a combination of macrolides (azithromicine, clarithromicine) plus ethambutol plus rifabutin/rifampicin**

Who to treat? (ATS/IDSA 2020)

- In patients who meet the diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting
 - **especially in the context of positive acid-fast bacilli sputum smears**
 - **and/or cavitary lung disease**

(conditional recommendation, very low certainty in estimates of effect).
- The decision to initiate antimicrobial therapy for NTM pulmonary disease should be individualized based on a combination of clinical factors, the infecting species, and individual patient priorities

Susceptibility testing (ATS/IDSA)

- Few NTM (eg, *M kansasii*) have clinical response correlation with susceptibility tests:
 - Presence of inducible macrolide resistance (*erm41* gene) correlates with *M abscessus* treatment outcomes
 - Macrolide and amikacin susceptibilities correlate with MAC treatment response

- **MAC susceptibility-based treatment for macrolides and amikacin over empiric therapy**
- ***M. kansasii* susceptibility-based treatment for rifampicin over empiric therapy**
- ***M. xenopi* insufficient evidence**
- ***M. abscessus* susceptibility-based treatment for macrolides and amikacin over empiric therapy**

3. Terapia

1. Concentrazioni sub-ottimali (←TB)

- Pochi studi PK – Cmax di azitromicina!
- Rifamicine spesso sottodosate (TB: diabetici, HIV+, basso peso)

2. Interazioni farmacologiche (← HIV&TB)

- Immunosoppressori

3. Infiammazione e concentrazioni intracellulari (←HIV)

Recommended Treatments (ATS/IDSA 2020) at least 12 months after sputum culture conversion

	MAC	<i>M. kansasii</i>	<i>M. xenopi</i>
I LINE	AZITRO + RIFAM + ETB 3 times/week + AMIKA if cavitory lesions or severe disease and daily regimen	RIFA + ETB + INH (daily) or AZITRO (3 times/week if non severe and non cavitory)	RIFA + ETB + AZITRO or MOXI + AMIKA if cavitory lesions or severe disease and daily regimen
II LINE	If Macro-R or failure after 6 months + ALIS*	If RIFA-R or intolerance + MOXI	

*amikacin liposome inhalation suspension (ALIS)

Recommended Treatments (ATS/IDSA 2020) at least 12 months after sputum culture conversion

M. abscessus

Macrolide Susceptibility Pattern

Mutational ^a	Inducible ^b	No. of Drugs ^c	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial phase ≥ 3	<i>Parenteral (choose 1–2)</i> Amikacin Imipenem (or Cefoxitin) Tigecycline <i>Oral (choose 2)</i> Azithromycin (clarithromycin) ^d Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	<i>Oral/inhaled (choose 2–3)</i> Azithromycin (clarithromycin) ^d Clofazimine Linezolid Inhaled amikacin	
Susceptible	Resistant	Initial phase ≥ 4	<i>Parenteral (choose 2–3)</i> Amikacin Imipenem (or Cefoxitin) Tigecycline <i>Oral (choose 2–3)</i> Azithromycin (clarithromycin) ^e Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	<i>Oral/inhaled (choose 2–3)</i> Azithromycin (clarithromycin) ^e Clofazimine Linezolid Inhaled amikacin	
Resistant	Susceptible or resistant	Initial phase ≥ 4	<i>Parenteral (choose 2–3)</i> Amikacin Imipenem (or Cefoxitin) Tigecycline <i>Oral (choose 2–3)</i> Azithromycin (clarithromycin) ^e Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation Phase ≥ 2	<i>Oral/inhaled (choose 2–3)</i> Azithromycin (clarithromycin) ^e Clofazimine Linezolid Inhaled amikacin	

*amikacin liposome inhalation suspension (ALIS)

Predictors of anti-NTM treatment start

Respiratory Medicine 179 (2021) 106341



Contents lists available at ScienceDirect

Respiratory Medicine

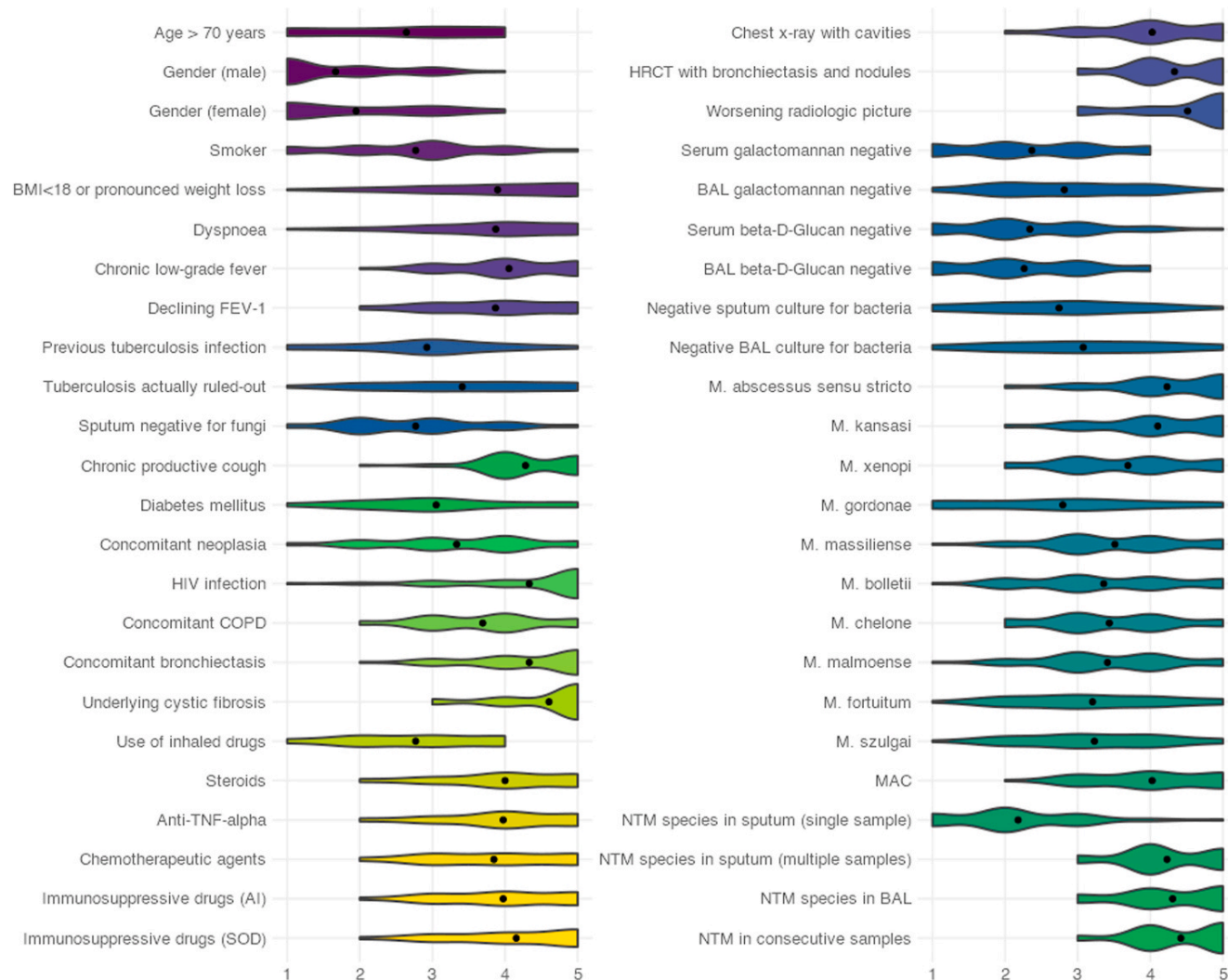
journal homepage: <http://www.elsevier.com/locate/rmed>



Short communication

Predictors of starting antimicrobial treatment in patients with nontuberculous mycobacterial lung disease in the Italian scenario: A SITA GIOVANI-IRENE promoted web-survey

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Outcome – NTM-LD

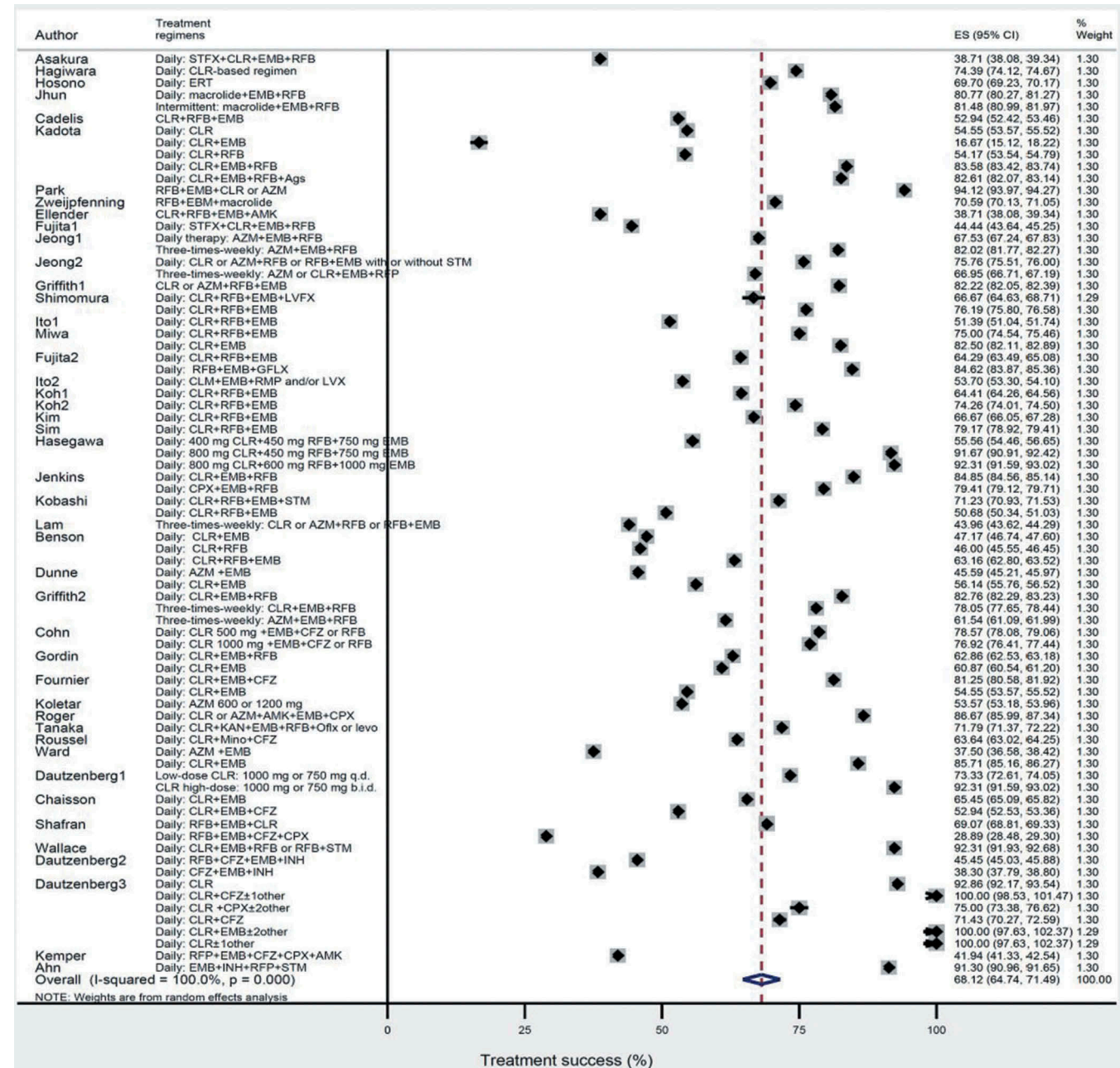
MAC (n=170)	RE	REH
No.	37	38
Deaths (All causes)	32%	39%
Deaths (Myco)	0%	8%
Failure/relapse	41%	16%
Alive and cured at 5 yrs	27%	34%

Jenkins PA, et al. Thorax 2008

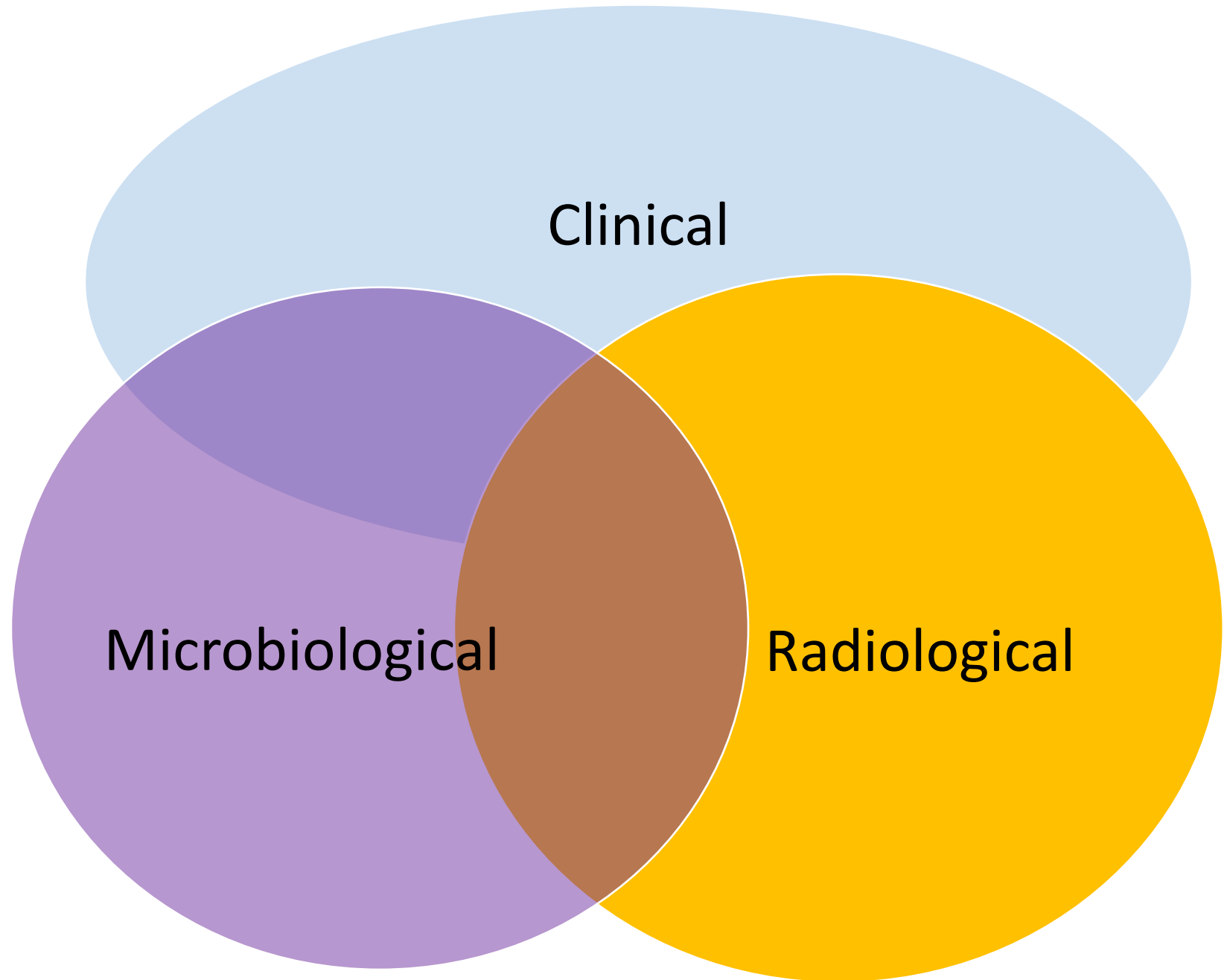
Outcome – NTM-LD

1. Macrolide-containing regimens led to better treatment success rates comparing to non-macrolide-containing regimens (69% vs 58.5%)
2. Treatment duration of 12 months or more showed better results.

Nasiri MJ, et al. Exp Rev Anti-inf Ther 2020

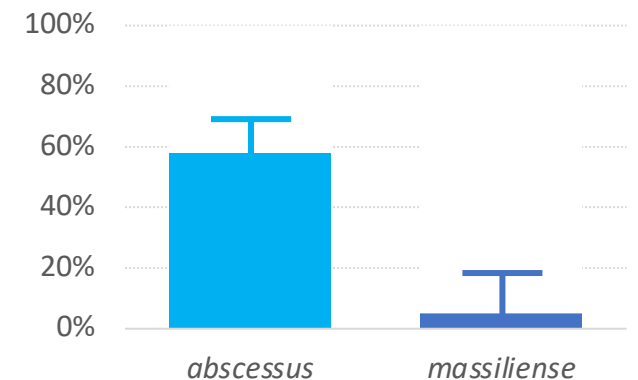
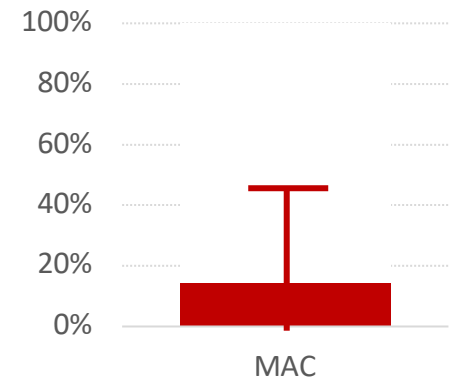


Failure

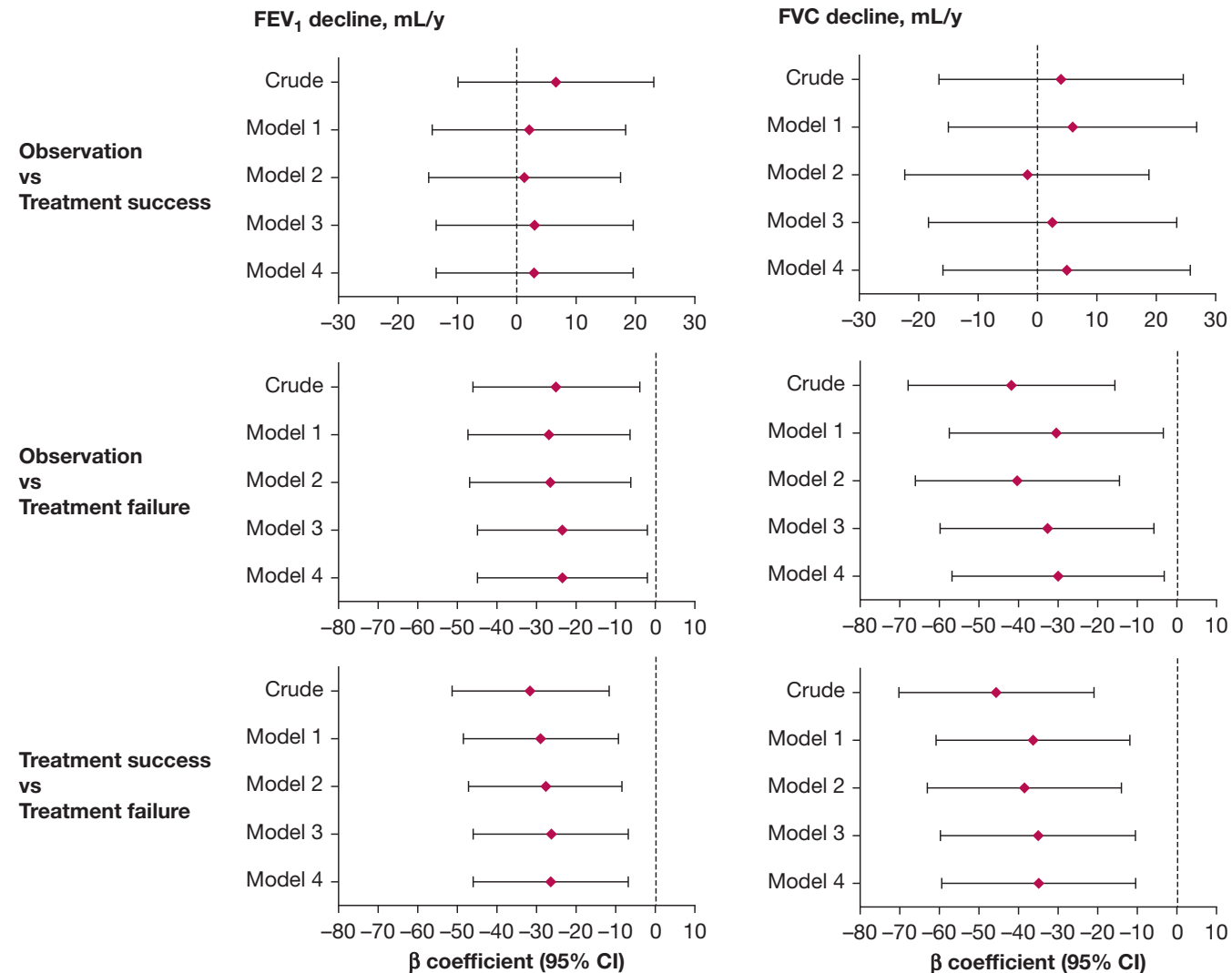


Failure and/or relapse

- **MAC-PD 13-16%** with 3-drug regimens
 - Up to 48% in some case series, **75% reinfection**
 - **Higher incidence if previously treated, macrolide resistant, non sputum conversion at 6 months**
 - Better outcomes by adding «new» drugs (fluoroquinolones, clofazimine, linezolid)
- **M. Abscessus-PD 42%** with standard treatment (4 weeks i.v. plus maintenance)
 - **75% in *Myc abs abscessus*** vs. 22% in *Myc abs massiliense*
 - 24-42% con 1/2 iv drugs → **58% in *Myc abs abscessus*** vs. 5% in *Myc abs massiliense*
 - 52% in the US



Lung Function Decline in NTM-LD

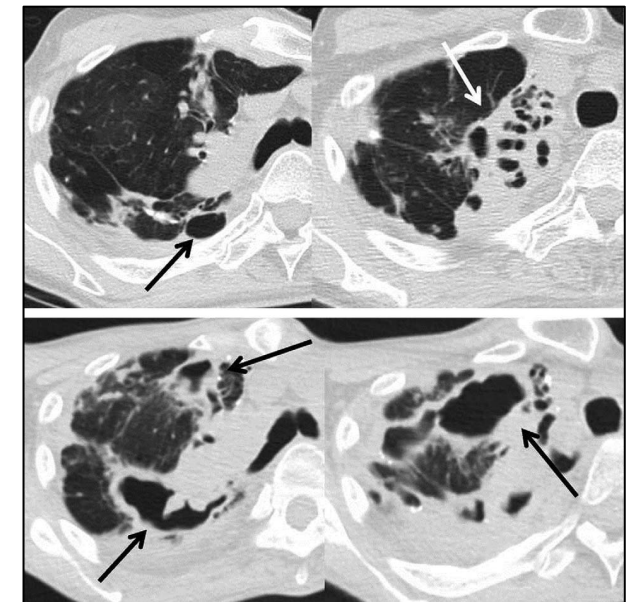


Computed tomographic findings of macrolide-resistant *Mycobacterium massiliense* pulmonary disease and changes after antibiotic treatment

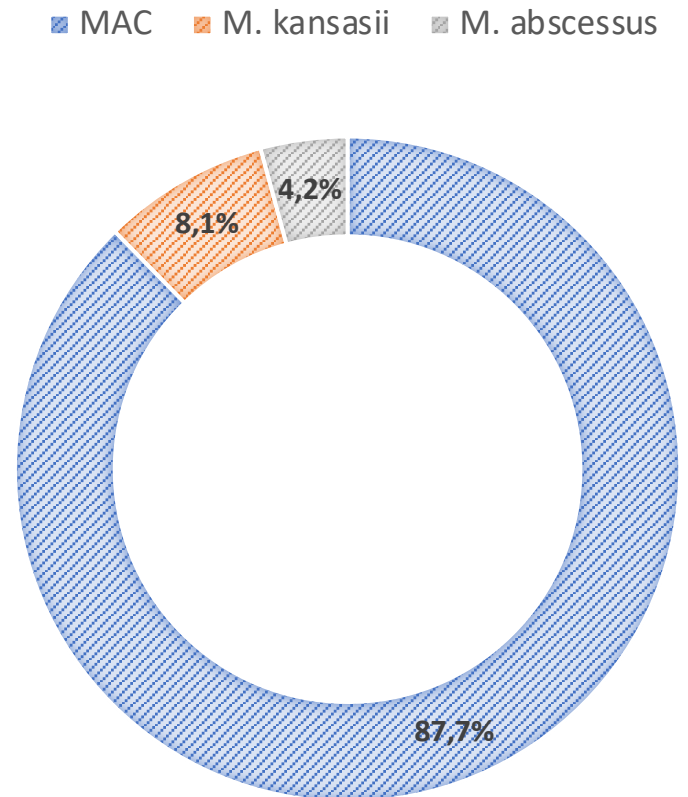
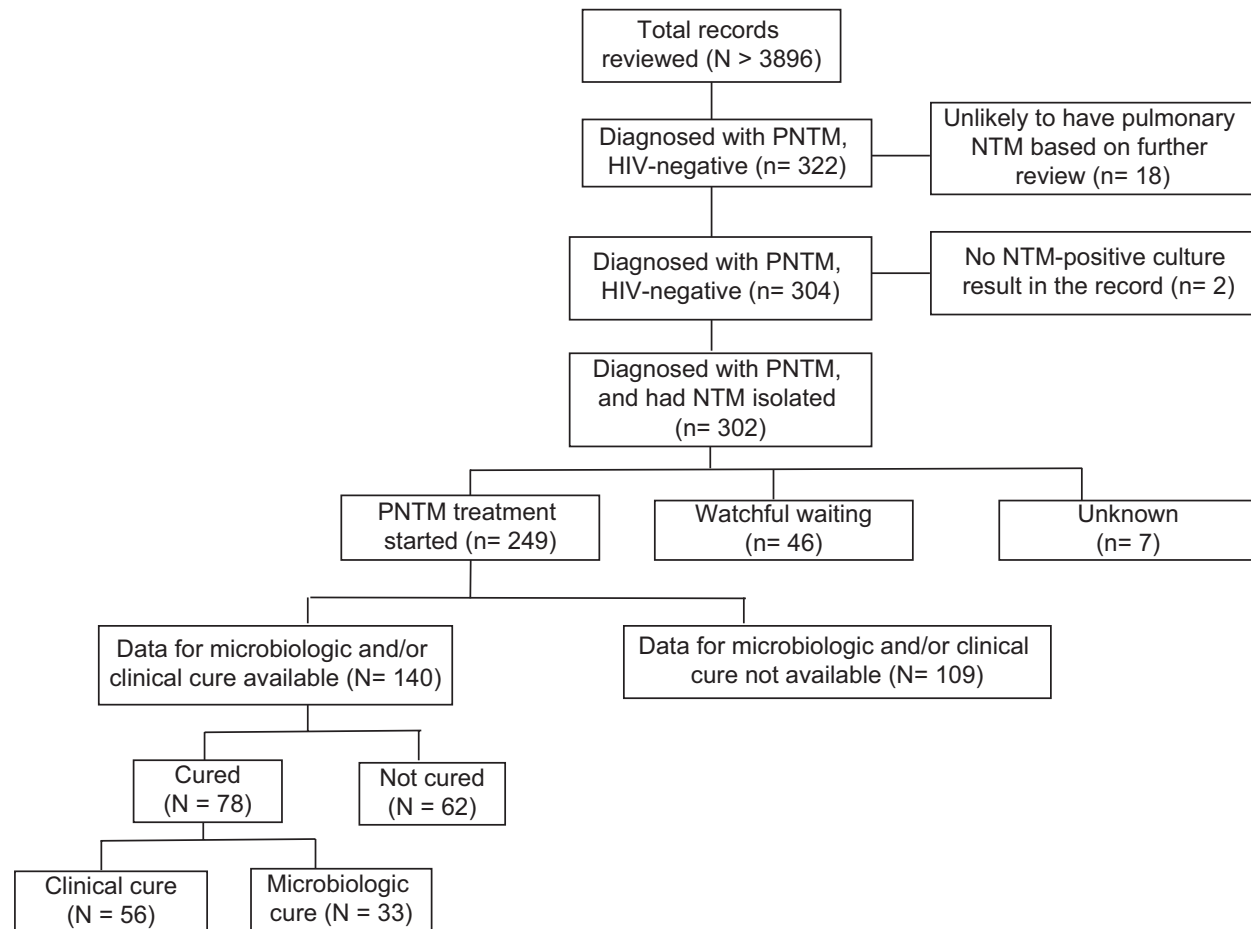
Hyun Jung Yoon, MD^{a,b}, Myung Jin Chung, MD^{a,*}, Won-Jung Koh, MD^c, Byung Woo Jhun, MD^c, Seong Mi Moon, MD^d

- 2 (11%) patients achieved sputum culture conversion during the follow-up period.
- On the last follow-up CT, overall CT scores were increased in 8 (62%) of 13 patients, and **total mean CT score was significantly increased** ($P=.021$). For each CT pattern, the cavity showed the greatest increase in CT score ($P=.027$), followed by bronchiectasis ($P=.038$).

FEW PATIENTS RECEIVED 2
IV DRUGS AND THEN
MACROLIDE + 2-4 DRUGS



Variability in the Management of Adults With Pulmonary Nontuberculous Mycobacterial Disease



Variability in the Management of Adults With Pulmonary Nontuberculous Mycobacterial Disease

Table 4. Treatment and Clinical Course of Patients With Pulmonary Nontuberculous Mycobacteria Negative for Human Immunodeficiency Virus

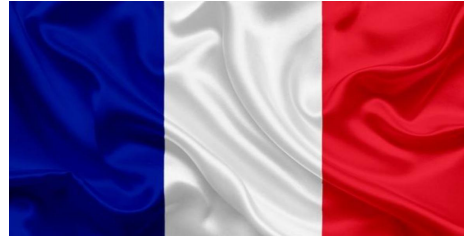
	All (N = 297)	MAC (n = 247)	<i>M. kansasii</i> (n = 23)	<i>M. abscessus</i> (n = 12)	Other (n = 7)	Multiple (n = 8)
Treated	245 (83.1)	203 (82.9)	21 (91.3)	9 (75)	6 (85.7)	6 (75)
No. of antibiotics administered as initial therapy						
1	10 ^a (4.1)	8 (3.9)	...	2 (22.2)	...	...
2	26 (10.6)	22 (10.8)	1 (4.8)	2 (22.2)	1 (16.7)	...
≥3	210 (85.4)	174 (85.3)	20 (95.2)	5 (55.6)	5 (83.3)	6 (100)
Mode of initial antibiotics administration						
Oral only	229 (93.1)	192 (94.1)	21 (100)	4 (44.4)	6 (100)	6 (100)
Oral and parenteral	17 (6.9)	12 (5.9)	...	5 (55.6)	...	...
Duration of treatment, mean ± SD, m	13.7 ± 9.7	13.7 ± 10.0	13.6 ± 8.0	13.4 ± 12.2	17.2 ± 3.3	10.9 ± 7.3
Adherence to ATS/IDSA treatment guidelines	99 (33)	88 (35.6)	4 (17.4)	2 (16.7)	1 (14.3)	3 (37.5)
Change in treatment	97 (32.7)	80 (32.4)	5 (21.7)	7 (58.3)	2 (28.6)	3 (37.5)
Reason for discontinued treatment						
Persistent positive culture	12 (7.5)	12 (9.3)	...	...	...	...
Culture-confirmed drug resistance	9 (5.7)	9 (7)	...	...	...	...
Adverse drug effects	90 (56.6)	75 (58.1)	3 (23.1)	6 (85.7)	1 (25)	5 (83.3)
Drug interaction	3 (1.9)	2 (1.6)	...	...	...	1 (16.7)
NTM culture result available at follow-up						
12–24 m	141 (47.5)	114 (46.2)	11 (47.8)	9 (75)	3 (42.9)	4 (50)
24–30 m	66 (22.2)	56 (22.7)	1 (4.3)	5 (41.7)	2 (28.6)	2 (25)
>30 m	41 (13.8)	35 (14.2)	3 (13)	2 (16.7)	...	1 (12.5)
NTM culture negative at follow-up						
12–24 m	88 (62.4)	70 (61.4)	11 (100)	3 (33.3)	2 (66.7)	2 (50)
24–30 m	36 (54.5)	30 (53.6)	1 (100)	3 (60)	1 (50)	1 (50)
>30 m	22 (53.7)	18 (51.4)	2 (66.7)	2 (100)	...	...
Symptoms improvement						
3 m	104 (44.6)	85 (43.4)	11 (68.8)	4 (50)	2 (33.3)	2 (28.6)
6 m	76 (41.3)	66 (41.3)	5 (50)	3 (42.9)	2 (66.7)	...
9 m	69 (41.1)	65 (44.8)	2 (20)	1 (14.3)	1 (25)	...
12 m	55 (34.6)	49 (34.5)	4 (50)	1 (25)	...	1 (25)
18 m	75 (36.2)	66 (38.2)	6 (37.5)	...	2 (40)	1 (20)
30 m	50 (29.6)	42 (28.8)	3 (37.5)	3 (42.9)	...	2 (40)
Hospitalization	83 (29.2)	62 (26.3)	9 (40.9)	6 (50)	3 (50)	3 (37.5)
Died	44 (15.7)	34 (14.7)	4 (18.2)	4 (33.3)	...	2 (25)
Total person-years follow-up	506	428	32	21	12	13
Months of follow-up, median (IQR)	24.2(14.5, 29.7)	24.8(15.0, 29.7)	17.5(13.8, 24.0)	26.1(14.4, 29.8)	24.4(20.7, 29.9)	23.4(9.0, 29.5)

Variability in the Management of Adults With Pulmonary Nontuberculous Mycobacterial Disease

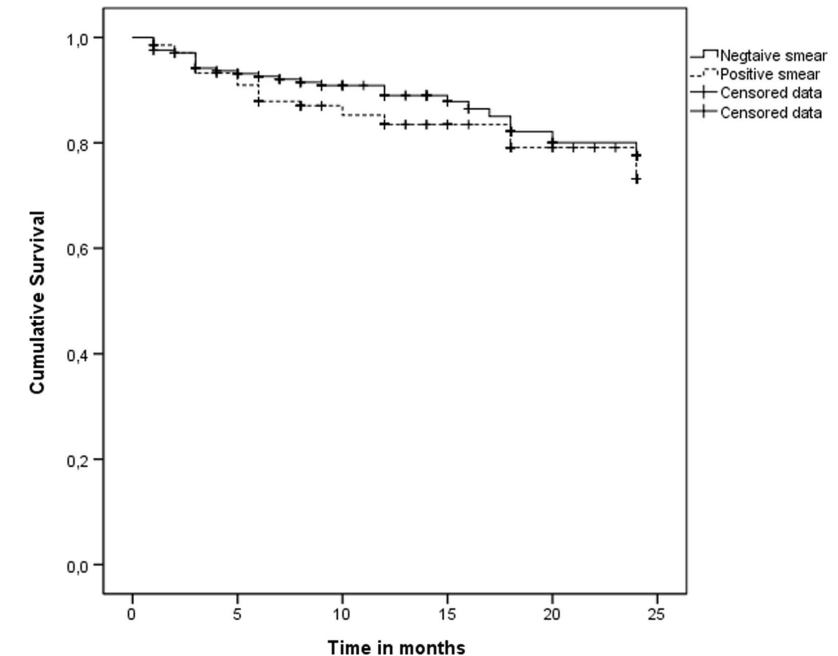
Factors Associated With Clinical and/or Microbiologic Cure					
	Cure (n=78)	No Cure (n=60)	p	Odds ratio	95%CI
Adherence toATS/ IDSA GLs	85.3%	55.9%	.000	4.583	2.017-10.411
Number of ATBs for initial therapy					
1	-	6.8%	.006	-	-
2	6.4%	16.9%			
3	93.6%	76.3%			

Characteristics of HIV- Patients With Pulmonary MAC Who Died Compared With Those Who Survived					
	Died (n=34)	Survived (n=187)	p	Odds ratio	95%CI
Female sex	47.1%	72.2%	.005	.342	.162-.722
Bronchiectasis	19.4%	38.8%	.042	.379	.147-.977
History of treated TB	12.9%	0.6%	.003	-	-
CKD	16.1%	3.1%	.012	5.963	1.613 - 22.040
Weight loss	51.5%	23.6%	.003	3.433	1.587 - 7.424
Rx findings					
Infiltrates/opacities	45.5%	26.9%	.040	2.259	1.051 - 4.859
Cavitation	48.5%	21.6%	.002	3.425	1.576 - 7.441
Tree-in-bud opacities	12.5%	40%	.002	.214	.072 - .639
Duration of treatment	9.2	14.2	.005	.917	.864 - .973

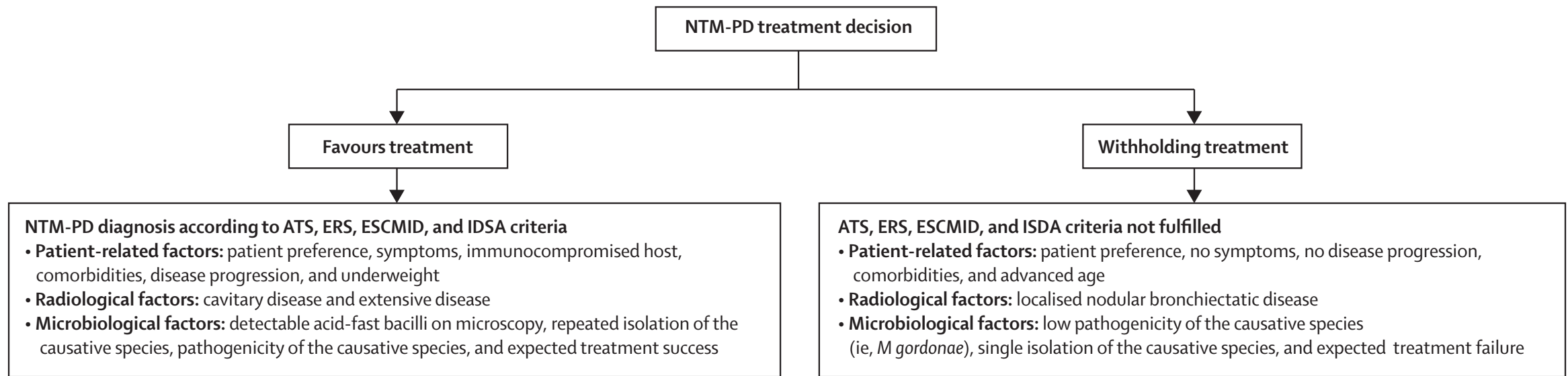
NTM-LD Cohort in



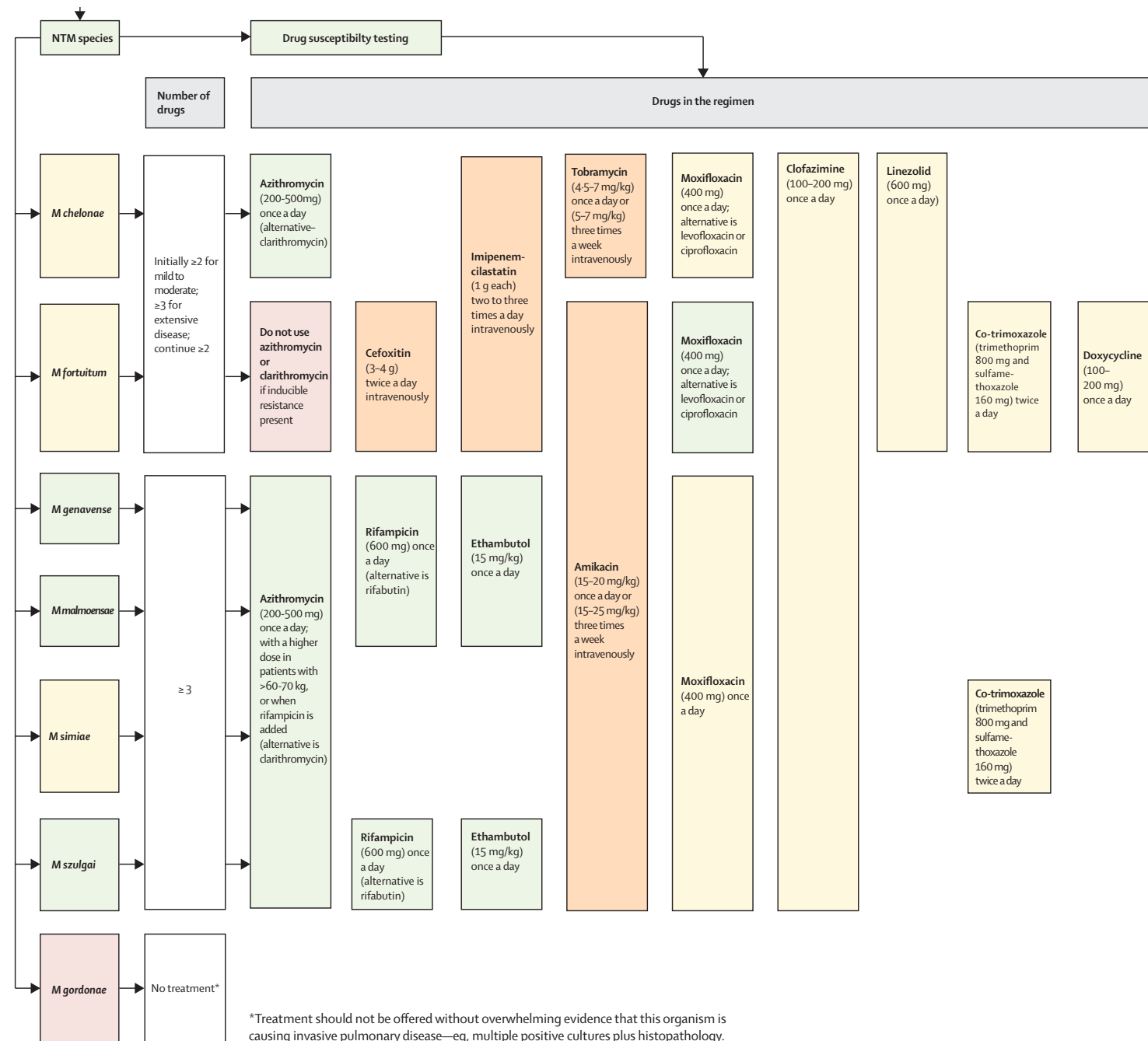
- 477 patients
- Respiratory comorbidities were found in 68% of cases, tuberculosis sequelae in 31.4% of patients, and immunosuppression in 16.8% of cases.
- The three most common NTM species were *Mycobacterium avium* complex (60%), *M. xenopi* (20%) and *M. kansasii* (5.7%).
- **Smear-positive was found in one third of NTM-PD.**
- Nodulobronchiectatic forms were observed in 54.3% of cases, and cavitory forms in 19.1% of patients.
- Sixty-three percent of patients were treated, 72.4% of patients with smear-positive samples, and 57.5% of patients with smear-negative samples.
- **Treatment was in adequacy with ATS guidelines in 73.5%.**
- The 2-year mortality was 14.4%. **In the Cox regression, treatment (HR = 0.51), age (HR = 1.02), and *M. abscessus* (3.19) appeared as the 3 significant independent prognostic factors.**



Consensus for treating less common NTM



Consensus for treating less common NTM



SINERGY

MAC

Amikacin + clofazimine

Avibactam + ceftazidime

MABS

Clarithromycin + linezolid +/- FQ

Clarithromycin + vancomycin

Clarithromycin + Rifabutin + FQ

Tigecycline + linezolid

Bedaquiline + Clofazimine

Avibactam +
amoxicilline/ceftaroline/imipenem/ertapenem

M. marinum case series

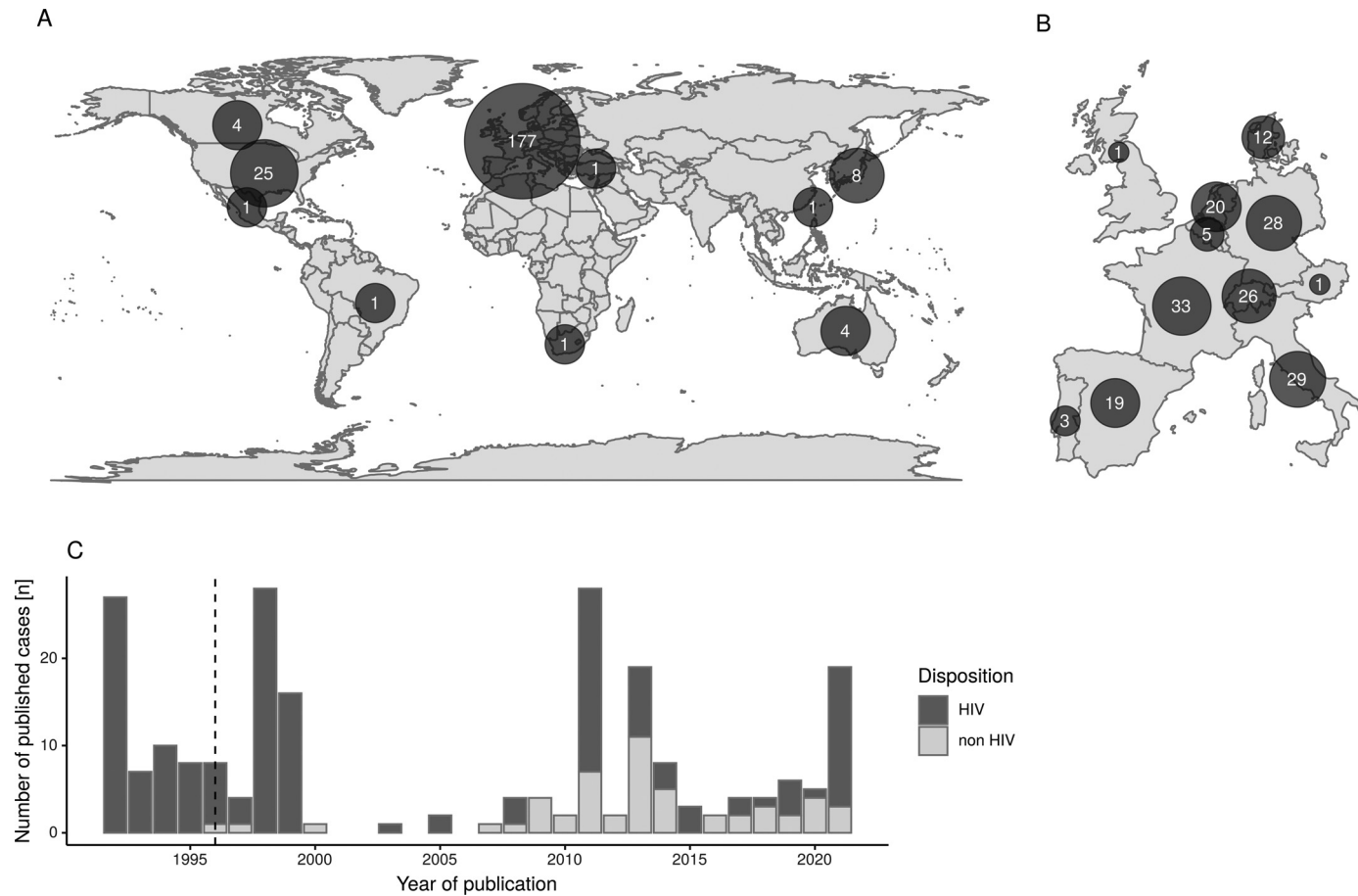
- Retrospective, culture-confirmed *M. marinum*, Netherlands, 2011–2018
- 40 cases
 - Fish tank 83%, swimming 7%
- **Antibiotic treatment cured 36/40 patients (90%)** after a mean treatment duration of 25 weeks.
 - Failure/relapse occurred in 3 patients, and 1 patient was lost to follow-up.
- Monotherapy in 35% and **2-drug therapy in 63%**.
 - Ethambutol–macrolide combinations (35%).
 - Eleven patients (28%) received additional surgery.
 - High rates of in vitro resistance to tetracyclines (36% of isolates).

Table 2. Treatment Regimens in 40 Patients Treated for *M. marinum* Disease

Initial Treatment	No. (%)
Doxycycline	10 (25)
Minocycline	4 (10)
Clarithromycin	6 (15)
Cotrimoxazole	1 (2.5)
EMB + CLA	8 (20)
EMB + AZI	3 (7.5)
RIF + EMB	3 (7.5)
RIF + CLA	3 (7.5)
RIF + EMB + CLA	1 (2.5)
RIF + EMB + AZI	1 (2.5)
Final Treatment Regimen	No. (%)
Doxycycline	4 (10)
Minocycline	3 (7.5)
Clarithromycin	5 (12.5)
Cotrimoxazole	2 (5)
EMB + CLA	11 (27.5)
EMB + AZI	3 (7.5)
RIF + EMB	6 (15)
RIF + CLA	3 (7.5)
CLA + DOX	2 (5)
RIF + EMB + AZI	1 (2.5)
Treatment duration	
Mean total treatment duration: 25 ± 14 wk	
Mean duration of treatment after clinical cure: 6 ± 3 wk	
Surgery	11 (28)

Abbreviations: AZI, azithromycin; CLA, clarithromycin; EMB, ethambutol; RIF, rifampicin.

Mycobacterium genavense individual patient meta-analysis



Mycobacterium genavense individual patient meta-analysis

- We included 223 patients (1992 to 2021).
- While the majority was HIV-positive ($n = 171$, 76.7%)
 - 52 patients were non-HIV-patients (23.3%), 36 of whom received immunosuppressive therapy (69%).
- We could confirm the bacterium's **tropism for the gastrointestinal tract with abdominal pain, hepato-/splenomegaly and abdominal lymphadenopathy** being major clinical manifestations.
- The regimens consisted mainly of macrolides, rifamycins and ethambutol.
- **Overall mortality was high**, but in logistic regression and time-to-event analysis a macrolide containing regimen was associated with better outcomes.

Table 3

Clinical manifestations, antimycobacterial treatments and overall outcome of included cases with *M. genavense* infection.

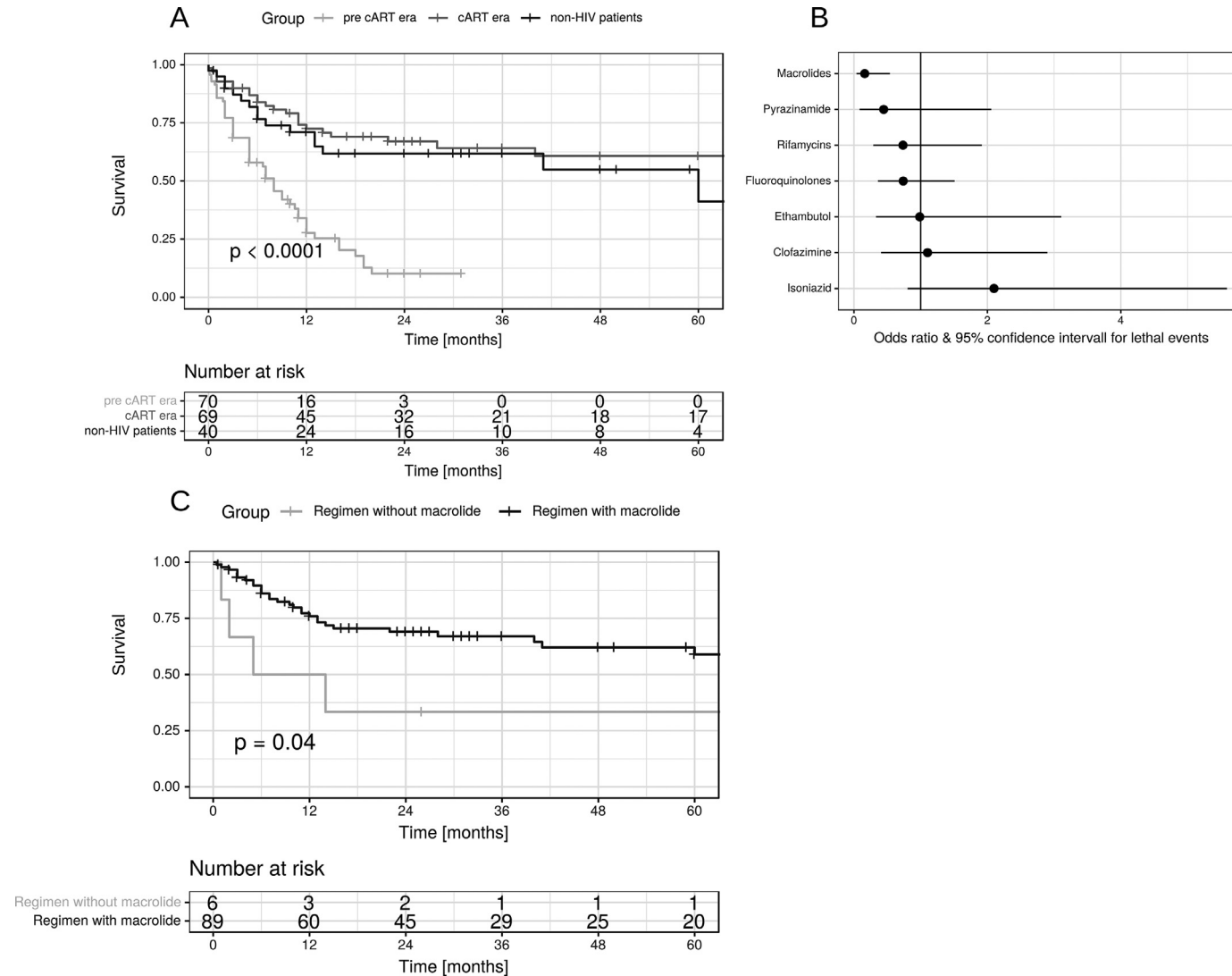
	all <i>M. genavense</i> cases ($n = 223$)		
	<i>n</i>	data available	[%]
Clinical Manifestations			
Fever	166	222	74.8
Weight Loss	133	222	59.9
Diarrhea	82	222	36.9
Abdominal pain	114	222	51.4
Chest pain	5	222	2.3
Hepatomegaly	74	222	33.3
Splenomegaly	81	222	36.5
Anemia	94	222	42.3
Lymphadenopathy	108	222	48.6
Abdominal	88	108	81.5
Thoracic	18	108	16.7
Cervical	15	108	13.9
Enteropathy	14	222	6.3
Sclerosing mesenteritis	6	222	2.7
Pulmonary symptoms	28	222	12.6
Pulmonary radiology	21	222	9.5
Pleural effusion	5	222	2.3
Ascites	10	222	4.5
Chyloascites	3	222	1.4
Chylothorax	2	222	0.9
Psoas abscessus	1	222	0.5
other clinical signs	36	222	16.2
NTM therapy			
Macrolide	186	205	90.7
Clarithromycin	127	149	85.2
Azithromycin	109	127	85.8
Rifamycin	23	127	18.1
Rifampicin	123	149	82.6
Rifabutin	63	123	51.2
Ethambutol	68	123	55.3
Guideline triple	132	149	88.6
Fluoroquinolone	91	149	61.1
Ciprofloxacin	71	149	47.7
Levofloxacin	39	71	54.9
Moxifloxacin	11	71	15.5
Ofloxacin/Sparfloxacin	20	71	28.2
Amikacin	3	71	4.2
Clofazimine	34	149	22.8
Isoniazid	28	149	18.8
Pyrazinamide	32	149	21.5
Linezolid	13	149	8.7
Others	3	149	2.0
Others	9	149	6.0
Deceased	95	195	48.7

Mycobacterium genavense individual patient meta-analysis

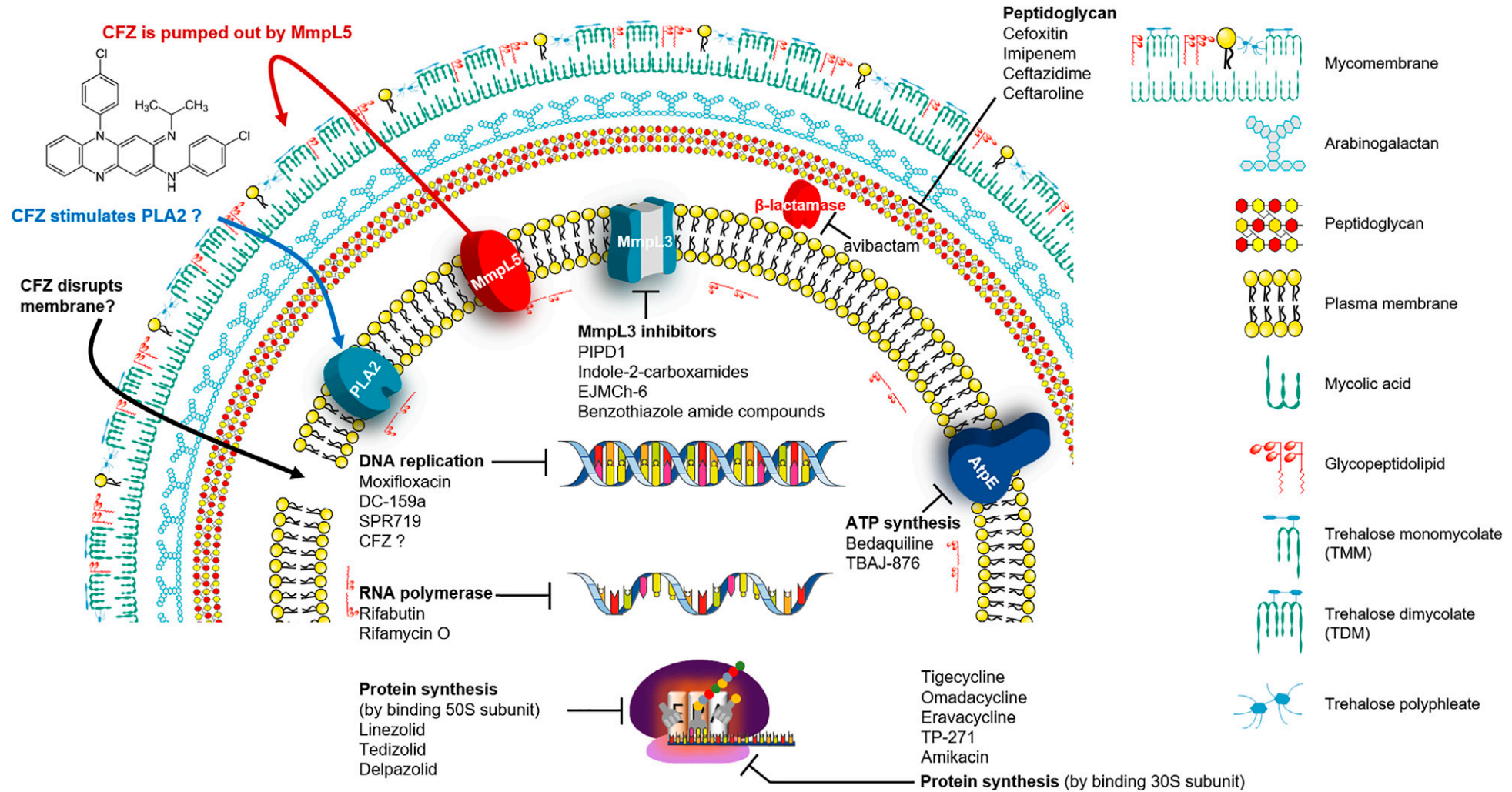


Fig. 3. FDG-PET/CT images of one of our patients suffering from disseminated *M. genavense* infection and HIV (not included in the analysis). The coronal view (A) and maximum intensity projection (B) show remarkable hepatosplenomegaly, abdominal enlarged lymph nodes as well as bone marrow involvement/activation with significantly increased glucose metabolism mirroring the predominant sites of infection of *M. genavense*.

Mycobacterium genavense individual patient meta-analysis



Drugs for Mabs (with pipeline)



Rifamycins for NTM

TABLE 1 MIC ranges and MIC₅₀ and MIC₉₀ values of four rifamycin derivatives for 311 clinical NTM isolates

NTM species (no.)	Antibiotic	No. (%) of isolates with MIC (μg/ml) of:												MIC range (μg/ml)	MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)
		≤0.062	0.125	0.25	0.5	1	2	4	8	16	32	64	>64			
<i>M. avium</i> (63)	Rifampin			2 (3.2)	2 (3.2)	6 (9.5)	16 (25.4)	8 (12.7)	7 (11.1)	2 (3.2)	3 (4.8)	11 (17.4)	6 (9.5)	0.25–>64	4	64
	Rifapentine		3 (4.8)	4 (6.3)	22 (34.9)	9 (14.3)	6 (9.5)	6 (9.5)	5 (7.9)	4 (6.3)	1 (1.6)		3 (4.8)	0.125–>64	1	16
	Rifaximin		1 (1.6)	2 (3.2)	2 (3.2)	15 (24)	19 (30.2)	10 (15.9)	4 (6.3)	6 (9.5)	1 (1.6)		3 (4.8)	0.125–>64	2	16
	Rifabutin	33 (52.4)	7 (11.1)	4 (6.3)	5 (7.9)	9 (14.3)	1 (1.6)	1 (1.6)				3 (3.2)		≤0.062–64	≤0.062	0.25
<i>M. intracellulare</i> (58)	Rifampin			1 (1.7)					1 (1.7)	1 (1.7)	11 (19)	41 (70.7)	3 (5.2)	0.25–>64	64	64
	Rifapentine	1 (1.7)					5 (8.6)	19 (32.8)	19 (32.8)	9 (15.5)	2 (3.4)	1 (1.7)	2 (3.4)	≤0.062–>64	8	16
	Rifaximin								1 (1.7)	2 (3.4)	12 (20.7)	41 (70.7)	2 (3.4)	8–>64	64	64
	Rifabutin	1 (1.7)	2 (3.4)	8 (12.7)	26 (44.8)	16 (28.4)	2 (3.4)	1 (1.7)		2 (3.4)				≤0.062–16	0.5	1
<i>M. kansasii</i> (58)	Rifampin				6 (10.3)	32 (55.2)	9 (15.5)	3 (5.2)	3 (5.2)		1 (1.7)	2 (3.4)	2 (3.4)	0.5–>64	1	8
	Rifapentine		14 (24.1)	30 (51.7)	5 (8.6)	4 (6.9)			2 (3.4)			1 (1.7)	2 (3.4)	0.125–>64	0.25	1
	Rifaximin			13 (22.4)	26 (44.8)	10 (17.2)	3 (5.2)	1 (1.7)	1 (1.7)			2 (3.4)	2 (3.4)	0.25–>64	0.5	4
	Rifabutin	51 (87.9)	1 (1.7)	3 (5.2)			1 (1.7)				1 (1.7)	1 (1.7)		≤0.062–64	≤0.062	≤0.062
<i>M. abscessus</i> (65)	Rifampin											1 (1.5)	64 (98.5)	64–>64	>64	>64
	Rifapentine										1 (1.5)	3 (4.6)	61 (93.8)	32–>64	>64	>64
	Rifaximin							1 (1.5)			2 (3.1)	18 (27.7)	44 (67.7)	4–>64	>64	>64
	Rifabutin			1 (1.5)			3 (4.6)	8 (12.3)	25 (38.5)	26 (40)	2 (3.1)			0.25–32	8	16
<i>M. massiliense</i> (67)	Rifampin		1 (1.5)				1 (1.5)	1 (1.5)				17 (25.4)	47 (70.1)	0.125–>64	>64	>64
	Rifapentine					1 (1.5)			3 (4.5)	4 (6)	5 (7.5)	33 (49.3)	21 (31.3)	1–>64	64	>64
	Rifaximin						4 (6)		5 (7.5)	6 (9)	19 (28.4)	31 (46.3)	2 (3)	2–>64	32	64
	Rifabutin	1 (1.5)		3 (4.5)		2 (3)	16 (23.9)	24 (35.8)	12 (17.9)	9 (13.4)				≤0.062–16	4	16

Rifamycins for NTM (2)

TABLE 2 MIC ranges and MIC₅₀ and MIC₉₀ values of four rifamycin antibiotics for 57 macrolide-resistant and 44 aminoglycoside-resistant clinical NTM isolates

		No. (%) of isolates with MIC (μg/ml) of:												MIC range (μg/ml)	MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)
NTM species (no.)	Antibiotic	≤0.062	0.125	0.25	0.5	1	2	4	8	16	32	64	>64			
Macrolide resistant																
<i>M. avium</i> (10)	Rifampin	1 (10)							1 (10)	1 (10)	1 (10)	2 (20)	4 (40)	≤0.062–>64	64	>64
	Rifapentine	1 (10)				1 (10)	1 (10)	1 (10)	3 (30)	1 (10)			2 (20)	≤0.062–>64	8	>64
<i>M. intracellulare</i> (17)	Rifaximin	1 (10)					1 (10)	3 (30)	1 (10)			2 (20)	2 (20)	≤0.062–>64	4	>64
	Rifabutin	1 (10)		3 (30)	2 (20)	3 (30)	1 (10)							≤0.062–2	0.5	2
	Rifampin	2 (11.8)		1 (5.9)						1 (5.9)	3 (17.6)	10 (58.8)		≤0.062–64	64	64
	Rifapentine	1 (5.9)	1 (5.9)	1 (5.9)				2 (11.8)	8 (47.1)	3 (17.6)		1 (5.9)		≤0.062–64	8	16
	Rifaximin	1 (5.9)	2 (11.8)							1 (5.9)	4 (23.5)	9 (52.9)		≤0.062–64	64	64
	Rifabutin	3 (17.6)			2 (11.8)	2 (11.8)	9 (52.9)			1 (5.9)				≤0.062–16	2	2
<i>M. abscessus</i> (13)	Rifampin										1 (7.7)	1 (7.7)	11 (84.6)	32–>64	>64	>64
	Rifapentine										2 (15.4)	2 (15.4)	9 (69.2)	32–>64	>64	>64
<i>M. massiliense</i> (17)	Rifaximin									3 (23)	3 (23)	3 (23)	4 (30.8)	16–>64	64	>64
	Rifabutin						5 (38.5)	3 (23)	4 (30.8)	1 (9)				2–16	4	8
	Rifampin										3	2 (11.8)	12 (70.6)	32–>64	>64	>64
	Rifapentine									2 (11.8)		4 (23.5)	11 (64.7)	16–>64	>64	>64
	Rifaximin							2 (11.8)	3 (17.6)	1 (5.9)	4 (23.5)	2 (11.8)	5 (29.4)	4–>64	32	>64
	Rifabutin				1 (5.9)	1 (5.9)	7 (41.8)	2 (11.8)	4 (23.5)	2 (11.8)				0.5–16	2	16
Aminoglycoside resistant																
<i>M. avium</i> (12)	Rifampin					1 (8.3)	5 (41.7)	1 (8.3)	1 (8.3)		1 (8.3)	3 (25)		1–64	2	64
	Rifapentine				7 (58.3)	1 (8.3)	1 (8.3)	1 (8.3)	2 (16.7)					0.5–8	0.5	8
	Rifaximin			2 (16.7)	3 (25)	2 (16.7)	2 (16.7)	1 (8.3)		2 (16.7)				0.25–16	1	16
<i>M. intracellulare</i> (17)	Rifabutin	7 (58.3)	1 (8.3)	1 (8.3)	3 (25)									≤0.062–0.5	≤0.062	0.5
	Rifampin				1 (5.9)					2 (11.8)	5 (29.4)	8 (47.1)	1 (5.9)	0.5–>64	32	64
	Rifapentine	1 (5.9)				1 (5.9)	3 (17.6)	5 (29.4)	3 (17.6)	3 (17.6)	1 (5.9)			≤0.062–32	4	16
	Rifaximin			1 (5.9)				1 (5.9)	1 (5.9)	4 (23.5)	3 (17.6)	5 (29.4)	2 (11.8)	0.25–>64	32	>64
<i>M. abscessus</i> (9)	Rifabutin	2 (11.8)		3 (17.6)	6 (35.3)	2 (11.8)	1 (5.9)	2 (11.8)	1 (5.9)					≤0.062–8	0.5	4
	Rifampin												9 (100)	>64	>64	>64
	Rifapentine											1 (11.1)	8 (88.9)	64–>64	>64	>64
	Rifaximin										2 (22.2)	7		32–64	64	64
<i>M. massiliense</i> (6)	Rifabutin						6 (66.7)	2 (22.2)	1 (11.1)					4–16	4	16
	Rifampin												6 (100)	>64	>64	>64
	Rifapentine											3 (50)	3 (50)	64–>64	>64	>64
	Rifaximin											5 (83.3)	1 (16.6)	64–>64	>64	>64
	Rifabutin						1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)				2–16	8	16

Rifabutin for Mabs?

- Rifampin shows poor growth inhibition of *M. abscessus* isolates (MIC, 128 mg/liter) due to the drug-modifying activity of its ADP-ribosyltransferase ArrMAB
 - Deletion of arrMab in *M. abscessus* isolates has been shown to decrease not only the MIC for RMP but also for two other rifamycins
- Rifabutin was identified in an *in vitro* *M. abscessus* drug screen and verified to be active against various *M. abscessus* strains (MIC, ≤ 3 mg/ liter).
- Subsequently, RBT proved to be efficacious in *in vitro* and *in vivo* models of *M. abscessus* infection, whereas RMP lacked activity

TABLE 1 MIC and relative resistance ratios of strains

Strain	RBT		RFX		RMP		TET		AMK	
	MIC ^a	RRR ^b	MIC ^a	RRR ^b	MIC ^a	RRR ^b	MIC ^a	RRR ^b	MIC ^a	RRR ^b
<i>M. abscessus</i>	4		32		128		32		1	
Δarr_{MAB}	1.1×10^{-5}	18	1.5	4	0.38	8	24	0	1	0
Δarr_{MAB} pMV361- <i>arr_{Mab}</i>	4	0	16	1	64	1	16	1	1	0
Δarr_{MAB} ΔMAB_{0857} ΔMAB_{3483}	4.6×10^{-5}	16	1.5	4	0.25	9	24	0	1	0
Δarr_{MAB} ΔMAB_{1496c}	4.6×10^{-5}	16	1.5	4	0.19	9	1	5	1	0

^aMedian of 6 replicates in mg/liter.

^b $\log_2 \text{MIC}_{\text{wt}}/\text{MIC}_{\text{comparator}}$

DDI with rifampicin and rifabutin

- Rifampicin powerful inducer of
 - Intestinal and liver CYP450 isoenzymes (PXR activation)
 - P-glycoprotein
- Rifabutin less powerful inducer but sensitive to CYP3A4 inhibition (boosted-PI/rifabutin DDI)
- Enzyme induction takes 2-4 weeks to reach its top and it may persist for 2-4 weeks after drug discontinuation

Drug/Drug Class	Comments
HMG-CoA Reductase Inhibitors (Simvastatin, Atorvastatin, Pravastatin)	Monitor lipid panel; increased dose will likely be needed for select HMG-CoA reductase inhibitors
Anticoagulants (Oral Coumarins)	Monitor international normalized ratio; increased anticoagulant dose will likely be needed
Contraceptives (Oral)	Use alternative form(s) of birth control; counsel patient and document in chart
Cyclosporine	Monitor serum cyclosporine concentrations; increased dosage will likely be needed
Digitoxin/Digoxin	Monitor arrhythmia control, signs and symptoms of heart failure, and serum digitoxin/digoxin concentrations
Glucocorticoids	Increase dose of glucocorticoid 2- to 3-fold
Itraconazole	Prefer to avoid use with rifampin; if must use, increase dose and monitor response
Ketoconazole	Avoid concomitant use if possible; if must use, increase dose and monitor response; space ketoconazole and rifampin doses by 12 h
Methadone	Increase methadone dose with concomitant rifampin; monitor and control withdrawal symptoms
Midazolam/Triazolam	Prefer to avoid use with rifampin; use another agent if possible
Phenytoin	Monitor serum phenytoin concentrations and seizure activity; increase dosage if needed
Propafenone	Monitor clinical response; increased dose may be needed, or use another agent if possible
Quinidine	Monitor serum quinidine concentrations and arrhythmia control; increase dosage if needed
Tacrolimus	Monitor serum tacrolimus concentrations and clinical response; increased dose may be needed, or use another agent if possible
Theophylline	Monitor serum theophylline concentrations; increase dosage if needed
Calcium Channel Blockers (Verapamil, Diltiazem, Nifedipine)	Alternative class of agents should be considered; dosage increase may be needed; monitor clinical response

DDI with rifampicin and rifabutin (2)

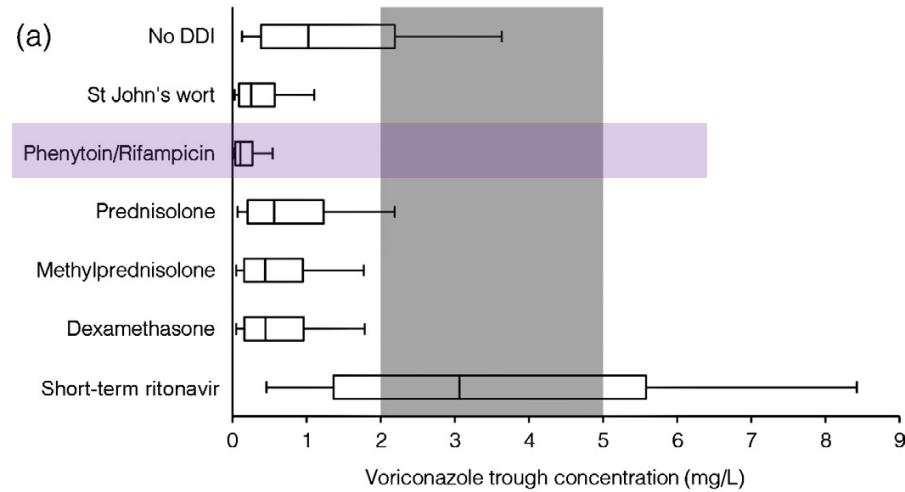
		Rifamycin observed or predicted effects on transporters and P450 enzymes expressed as AUC ratio (AUC in presence/absence of rifamycin)						
Rifamycin	Rifamycin pharmacokinetic characteristics	Transporters (probe drug used)		Key P450 Enzymes (probe drug used)				Other transporters/enzymes
		P-gp (total dabigatran)	BCRP (rosuvastatin)	1A2 (caffeine)	2C9 (S-warfarin)	2C19 (lansoprazole)	3A4 (midazolam)	
Rifampin	Metabolized by esterases Autoinduction of metabolism	0.33 ¹¹	Minimal ¹¹	0.61 ¹³	0.45 ¹³	0.16 ¹³	0.12 ¹³	Glucuronosyl-transferases Sulfotransferases CYP 2A6, 2B6, 2C8 OATP1B1, OATP1B3
Rifabutin	Metabolized by esterases and CYP3A4 Autoinduction of metabolism	0.81 ¹²	Minimal ¹²	0.98 ¹³	0.60 ¹³	0.22 ¹³	0.34 ¹³	OATP1B3
Rifapentine	Metabolized by esterases	Human data not available	Human data not available	Human data not available	Human data not available	Human data not available	0.07 ⁶³	

What would you do in a patient with bronchiectasis, symptoms, lung nodules, MAC and Aspergillus on BAL culture that needs antineoplastic chemotherapy?

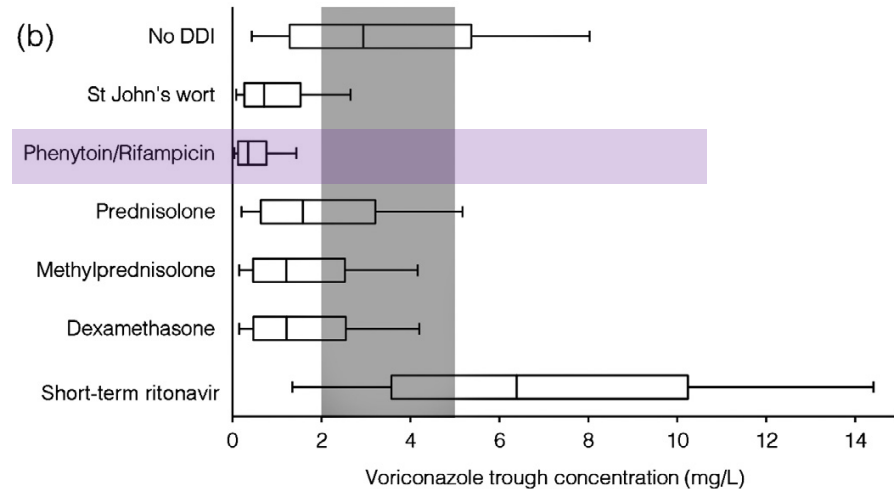
1. Treat Aspergillosis first and MAC afterwards
2. Treat Aspergillosis with voriconazole and MAC with rifampicin/ethambutol/azithromicine
3. Treat Aspergillosis with voriconazole and MAC with rifabutin/ethambutol/azithromicine
4. Treat Aspergillosis with voriconazole and MAC with moxifloxacin/ethambutol/azithromicine
5. Treat Aspergillosis with L-Amb and MAC with rifampicin/ethambutol/azithromicine

Voriconazole and rifamycins

No
CYP2C19
loss of
function
genes



1+
CYP2C19
loss of
function
genes



3 case reports of VORICO + RIFABUTIN
Vorico dosed 3 times/day after TDM

[CHEST Pearls]

CHEST

A 30-Year-Old Immune Deficient Woman With Persistent Cough and Shortness of Breath

Check for updates

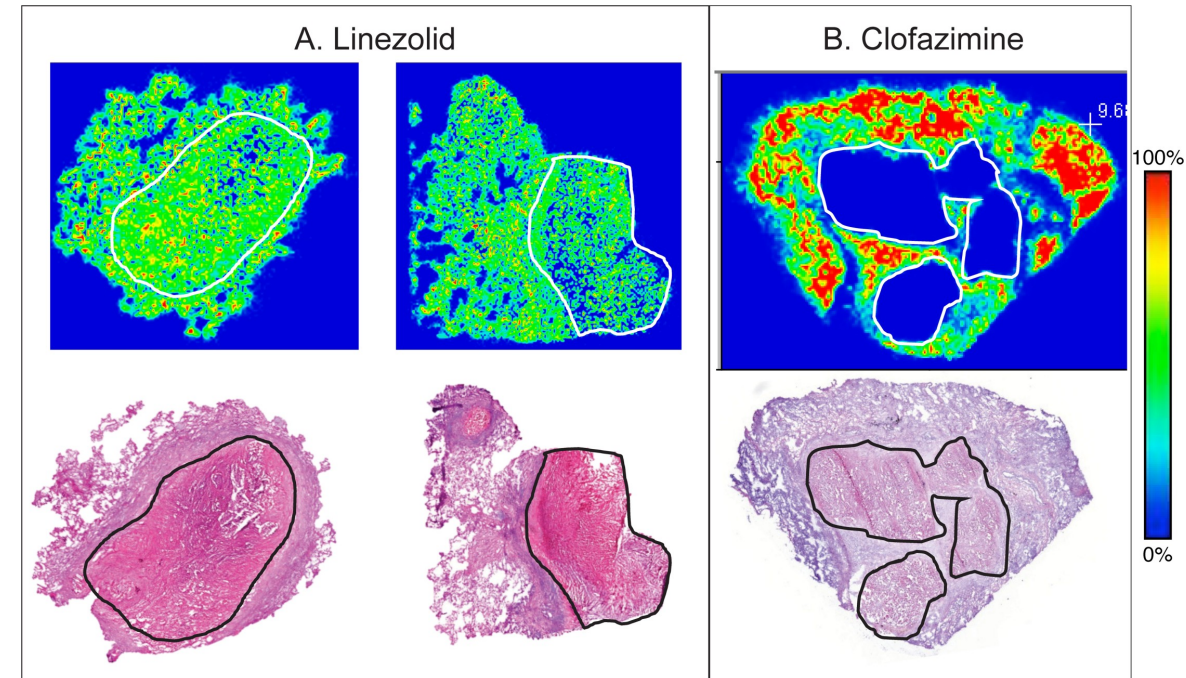
Daffolyn Rachael Fels Elliott, MD, PhD; Michael P. Combs, MD; Anil K. Attali, MD; and Carol F. Farver, MD

CASE PRESENTATION: A 30-year-old woman was referred with increasing shortness of breath and cough in the setting of GATA2 deficiency. She initially presented 9 years previously with recurrent episodes of pneumonia and sinusitis. Genetic testing revealed a heterozygous GATA2 mutation (c.988C>T). She has since had multiple infections that have included necrotizing fasciitis of the right thumb, recurrent pilonidal infections (which required 23 procedures), esophageal candidiasis, and human papillomavirus-positive high-grade squamous intraepithelial lesion of the cervix. Serial bone marrow biopsy specimens showed persistent hypocellularity (20% to 60%) with intermittent erythroid atypia and variable detection of trisomy 8, which were concerning for evolving myelodysplastic syndrome. One year before the current admission, she was diagnosed with disseminated *Mycobacterium avium* complex and was treated with rifabutin, ethambutol, and azithromycin. She was taking voriconazole, acyclovir, and trimethoprim-sulfamethoxazole prophylaxis.

CHEST 2021; 160(4):e343-e346

Clofazimina

- Farmaco molto lipofilo (volume di distribuzione 1470 litri) e con lunga emivita (fino a 70 giorni)
- Meccanismo incerto:
 - Si accumula nella parete cellulare dei batteri (o satura la componente lipidica)
 - Nessun effetto nei primi 7-14 giorni (TB)
 - Potenziale meccanismo immunomediato
 - Inibizione canali $K_v 1.3$ (aumento attività Linfociti T)



Clinical Outcomes of Clofazimine Use for Rapidly Growing Mycobacterial Infections

George B. Carey,¹ Pablo Tebas,² Christopher Vinnard,³ Deborah Kim,² Denis Hadjiliadis,⁴ John Hansen-Flaschen,⁴ Daniel Dorgan,⁴ Laurel Glaser,⁵ Grant Barton,⁶ and Keith W. Hamilton²

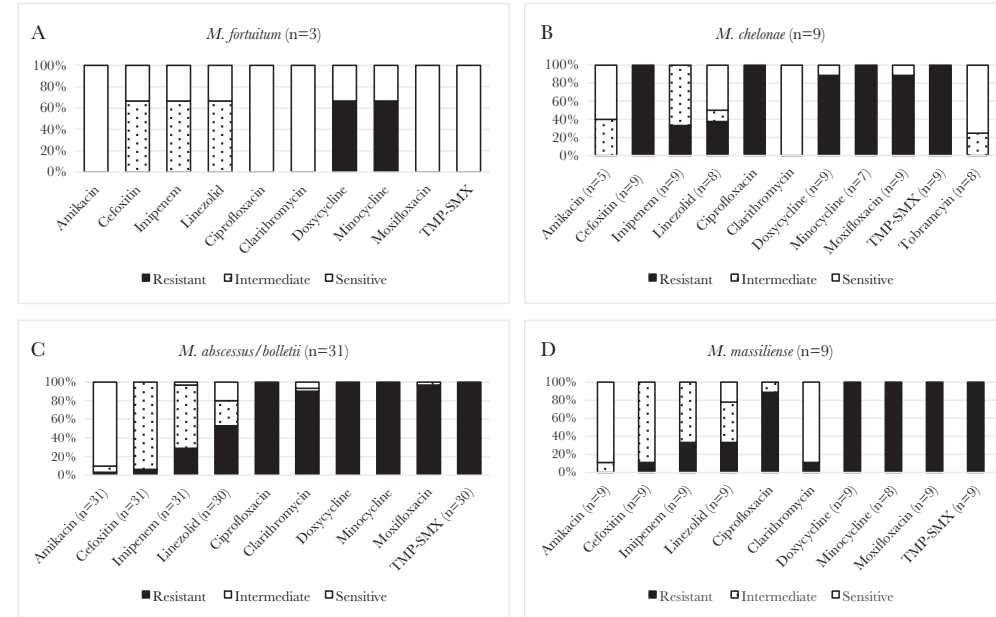
¹Department of Medicine, Yale-New Haven Hospital, New Haven, Connecticut, USA, ²Division of Infectious Diseases, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, ³Public Health Research Institute, New Jersey Medical School, Newark, New Jersey, USA, ⁴Division of Pulmonary, Allergy and Critical Care, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, ⁵Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, and ⁶Division of Internal Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

Background. Rapidly growing mycobacteria (RGM) have high rates of intrinsic antibiotic resistance and require prolonged antibiotic therapies associated with considerable toxicity. Less toxic and more effective therapies are needed. One promising agent is clofazimine (CFZ), an antibiotic with favorable in vitro data but limited clinical data in RGM.

Methods. We performed a retrospective cohort study of all patients treated for RGM infection with a CFZ-containing regimen in the University of Pennsylvania Health System between January 1, 2010, and December 31, 2016. The primary outcome was clinical cure, defined as no evidence of clinical or microbiologic infection recurrence 1 year after the completion of treatment. Secondary outcomes included clinical, radiologic, and microbiologic response; all-cause mortality; infection-specific mortality; and treatment-related adverse events. Descriptive and unadjusted analyses were performed to elucidate associations between pertinent demographic and comorbidity data, clinical presentation, treatment history, and treatment outcomes.

Results. We treated 55 patients with CFZ for RGM infection during the study period, in combination with a median of 5 other antibiotic agents during each treatment course. Clinical cure with initial treatment regimen was achieved in 43% of patients with pulmonary infection and 71% of patients with nonpulmonary infection. CFZ was well tolerated in our cohort and was discontinued prematurely in 20% of patients, but only in the context of discontinuing all antibiotic agents.

Conclusions. As part of multidrug therapy, CFZ is well tolerated and may be effective in patients with RGM infection, especially nonpulmonary and non-*Mycobacterium abscessus* complex infections.



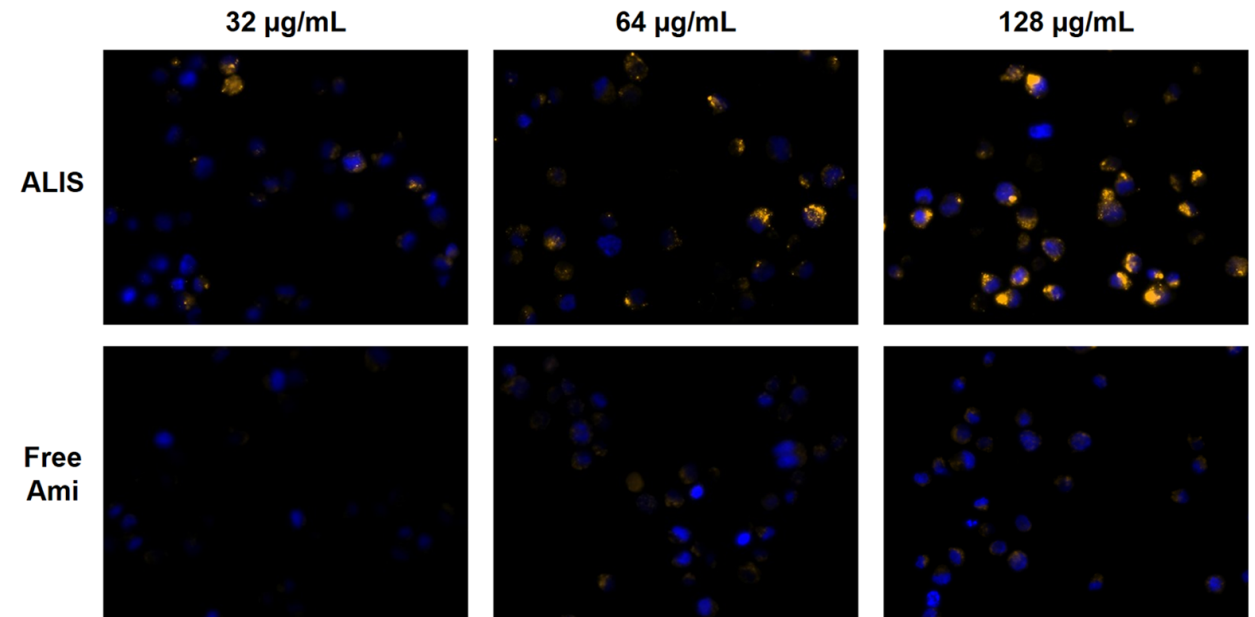
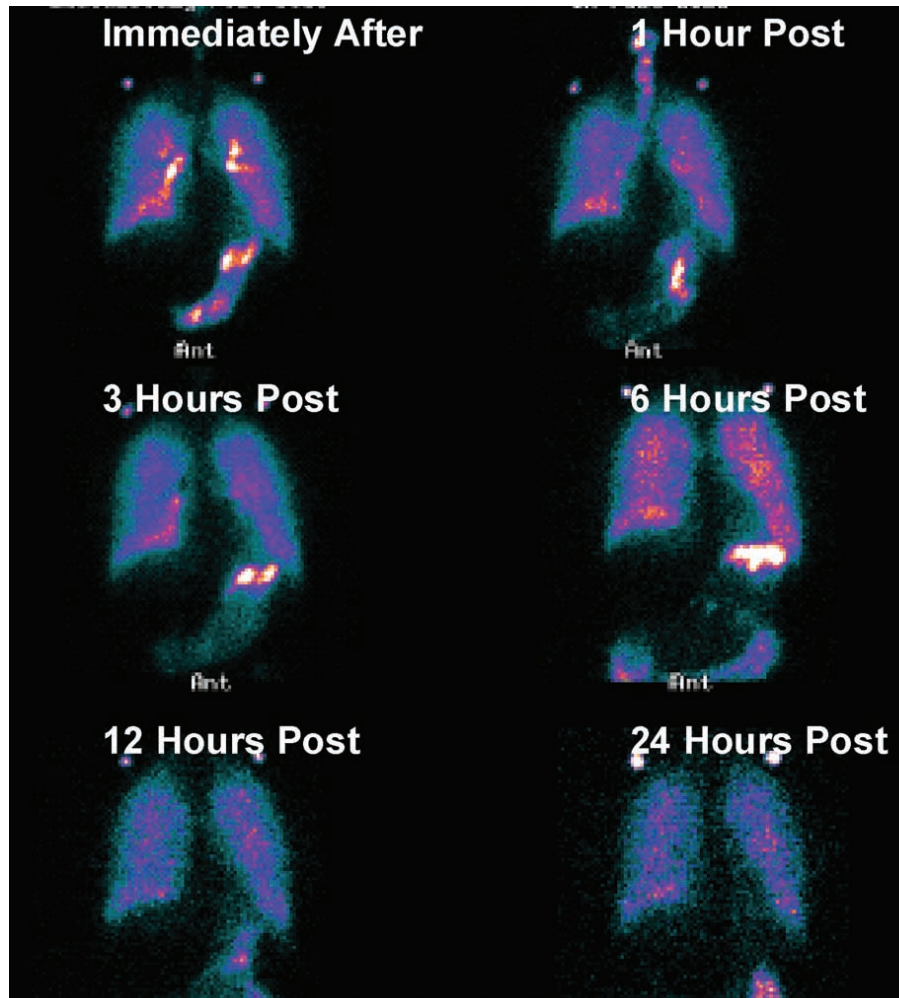
Cura “clinica” nel 43% dei casi

absence of clinical, microbiologic, or radiographic evidence of recurrent infection for ≥ 1 year after cessation of CFZ-containing therapy

Clofazimine – new data

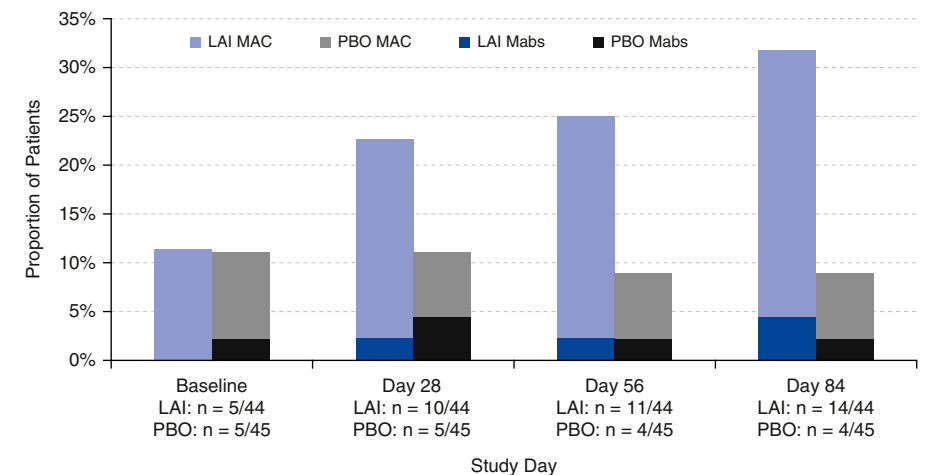
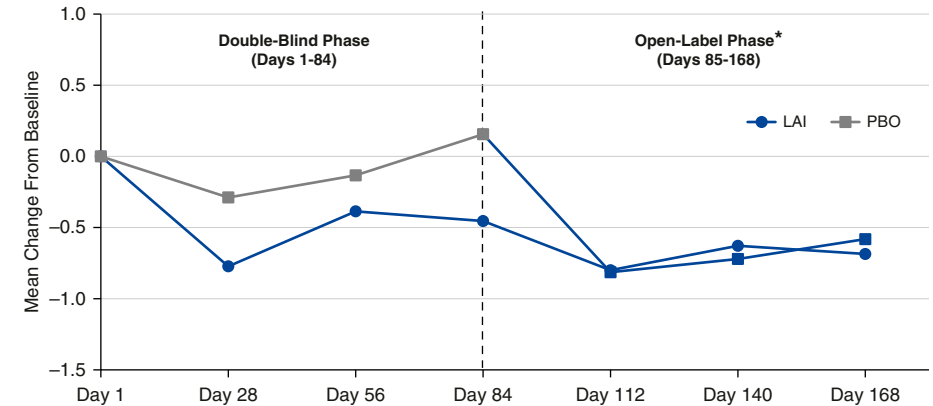
- Kim DH, et al. J Clin Med 2021
 - 238/303 isolates low MICs ($\leq 0.25 \mu\text{g/mL}$) including R-strains (47/57 and 32/35)
 - In 38 NTM-PD patients without resistance 47% achieved culture conversion (higher in the MIC $\leq 0.25 \mu\text{g/mL}$ group) vs. 20% in patients with CLA or AMK-R

Inhaled liposomal amikacin



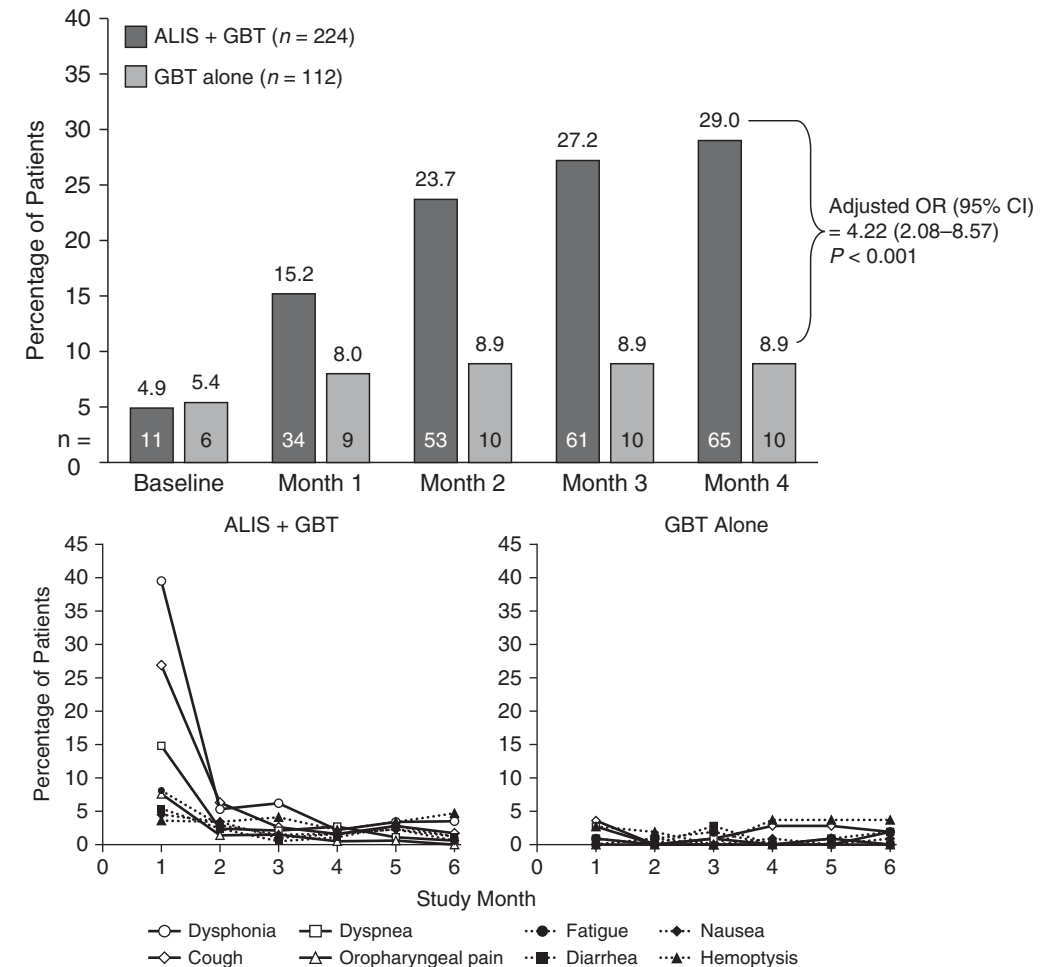
Amikacin liposome inhalation suspension (ALIS)

- Double-blind e poi open label, fase II
- 590 mg ALIS vs. placebo, 84 giorni in aggiunta a una multiterapia
- 89 pazienti con NTM-PD refrattaria
- 64% MAC, 36% MYC ABS
- Obiettivo primario non raggiunto ma obiettivi secondari microbiologici e funzionali a favore di ALIS (6MWT)
- Lieve aumento di tosse e disfonia nel braccio ALIS



Amikacin liposome inhalation suspension (ALIS)

- Open label, randomizzato, fase III
- ALIS + Guidelines-based treatment vs. GBT (2:1) (MAC-PD, dopo almeno 6 mesi di GBT)
- 224 ALIS + GBT vs. 112 GBT
- Conversione coltura in 29% (ALIS) vs. 8.9% (GBT) (OR 4.22, $p < 0.001$)
- **21.8% Claritro-R: conversione 13.7% vs. 4.5%**
- Aumento di tosse, dispnea e disfonia nel braccio ALIS (soprattutto primo mese)
 - Discontinuaizione $< 3\%$, SAEs non differenti
 - Tinnitus 7.6 vs. 0.9% (metà autorisoltisi)



BRIEF REPORT

Positive Effect of Liposomal Amikacin for Inhalation on *Mycobacterium abscessus* in Cystic Fibrosis Patients

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¹Cystic Fibrosis Center, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire de Montpellier, Univ Montpellier, France; ²Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Sorbonne Université, French Institute of Health and Medical Research (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; and ³Department of Microbiology, University Hospital of Montpellier, France

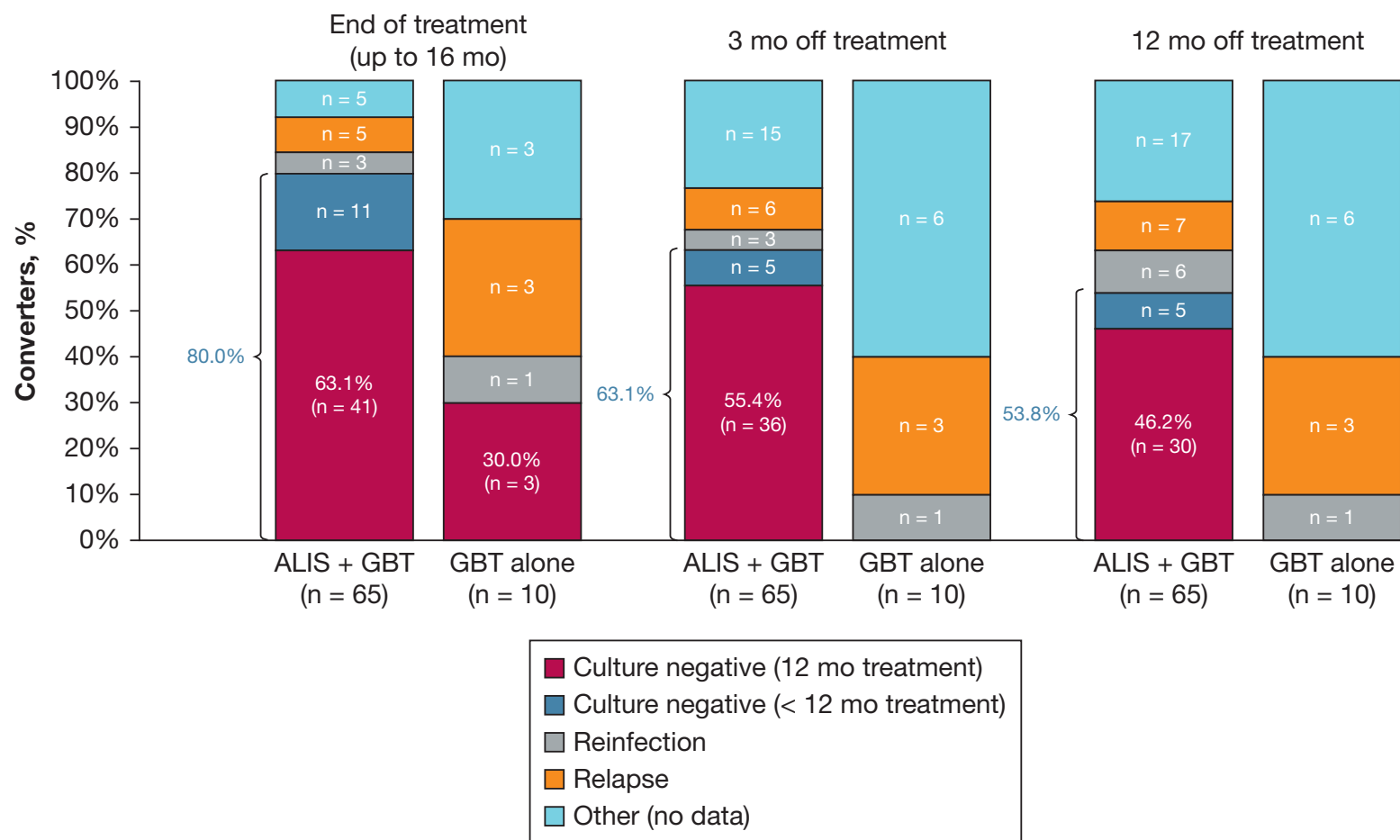
Mycobacterium abscessus is difficult to eradicate. At the Montpellier CF Center, we prescribed liposomal amikacin for inhalation to 5 patients with *M abscessus* infection. The 3 patients who completed the treatment did not have any respiratory exacerbation, showed negative cultures for *M abscessus* in their sputum, and stabilized their spirometric functions.

Table 1. Characteristics of the 5 Patients Treated With Liposomal Amikacin for Inhalation

Patient ID	Year of Birth	Genetic Mutations	First MAB Infection	Number of Positive MAB Cultures Before Treatment	First LAI Prescription	Treatment Compliance	Before LAI			After LAI (Most Recent Visit)					
							Body Mass Index (kg/m ²)	VEMS (% of Predicted Value)	FVC (% of Predicted Value)	Most Recent Visit at CF Center	Body Mass Index (kg/m ²)	VEMS (% of Predicted Value)	FVC (% of Predicted Value)	Positive MAB Cultures	Negative MAB Cultures
1*	2000	DF508/W846	12/2013	7	03/2016	Good	15.9	52%	71%	07/2017	17.4 (+1.5)	71% (+19%)	79% (+8%)	1 since 03/2016 0 after 09/2016	4 since 09/2016 (6 months treatment)
2	1983	DF508/R347P	05/2008	26	03/2016	Drop out after 2 months	17.4	27%	56%	06/2017	17.5 (+0.1)	25% (−2%)	51% (−5%)	9 since 03/2016	0
3*	1959	G542X/3849 + 10kb C > T	02/2011	11	04/2016	Good	18.6	33%	64%	05/2017	20.6 (+2.0)	34% (+1%)	66% (+2%)	1 since 04/2016 0 after 08/2016	3 since 08/2016 (4 months treatment)
4	1995	S364P/S364P	05/2016	14	12/2016	Drop out after 1 month	17.1	61%	83%	07/2017	16.8 (−0.3)	56% (−5%)	69% (−14%)	2 since 12/2016	0
5*	2005	DF508/DF508	05/2016	5	12/2016	Good	14.0	60%	65%	06/2017	16.0 (+2.0)	75% (+15%)	83% (+18%)	1 since 12/2016 0 after 01/2017	3 since 01/2017 (2 months treatment)

Amikacin Liposome Inhalation Suspension

Follow up of the CONVERT trial in sputum converters by month 6



Amikacin Liposome Inhalation Suspension

A 12-Month Open-Label Extension Clinical Trial

- Adults with refractory MAC lung disease not achieving culture conversion by CONVERT Month 6 could enroll in this open-label extension (INS-312) to receive 590 mg once-daily ALIS1GBT for 12 months.
- ALIS-naïve and prior-ALIS (max 8 months)

Characteristic	Total (N = 163)	ALIS-Naïve* Cohort (n = 90)	Prior-ALIS [†] Cohort (n = 73)
Age, mean (SD), years	64.8 (9.8)	64.8 (10.3)	64.9 (9.1)
Female, n (%)	105 (64.4)	54 (60.0)	51 (69.9)
Body mass index, mean (SD), kg/m ²	20.8 (3.8)	21.0 (3.6)	20.5 (4.0)
Race, n (%)			
White	101 (62.0)	60 (66.7)	41 (56.2)
Asian: Japanese	31 (19.0)	14 (15.6)	17 (23.3)
Asian: other	19 (11.7)	8 (8.9)	11 (15.1)
Black/African American	5 (3.1)	3 (3.3)	2 (2.7)
Multiracial	1 (0.6)	0 (0)	1 (1.4)
Not reported	6 (3.7)	5 (5.6)	1 (1.4)
Respiratory, thoracic, and mediastinal disorders, n (%) [‡]			
Bronchiectasis	116 (71.2)	65 (72.2)	51 (69.9)
COPD	42 (25.8)	27 (30.0)	15 (20.5)
Cough	42 (25.8)	16 (17.8)	26 (35.6)
Pulmonary cavitation	33 (20.2)	16 (17.8)	17 (23.3)
Dyspnea	22 (13.5)	13 (14.4)	9 (12.3)
Asthma	15 (9.2)	10 (11.1)	5 (6.8)
Hemoptysis	15 (9.2)	6 (6.7)	9 (12.3)
Pulmonary mass	14 (8.6)	9 (10.0)	5 (6.8)
Dysphonia	13 (8.0)	0 (0)	13 (17.8)
Emphysema	13 (8.0)	9 (10.0)	4 (5.5)
Clarithromycin-resistant MAC, n (%) [§]	42 (25.8)	17 (18.9)	25 (34.2)
Current smoker, n (%)	17 (10.4)	8 (8.9)	9 (12.3)
Duration of NTM disease, median (range), years	4.6 (0.8–33.2)	3.7 (0.8–19.6) [¶]	5.4 (0.8–33.2)

Amikacin Liposome Inhalation Suspension

A 12-Month Open-Label Extension Clinical Trial

Table 2. ALIS-naïve cohort: safety profile among patients who added ALIS at baseline (safety population)

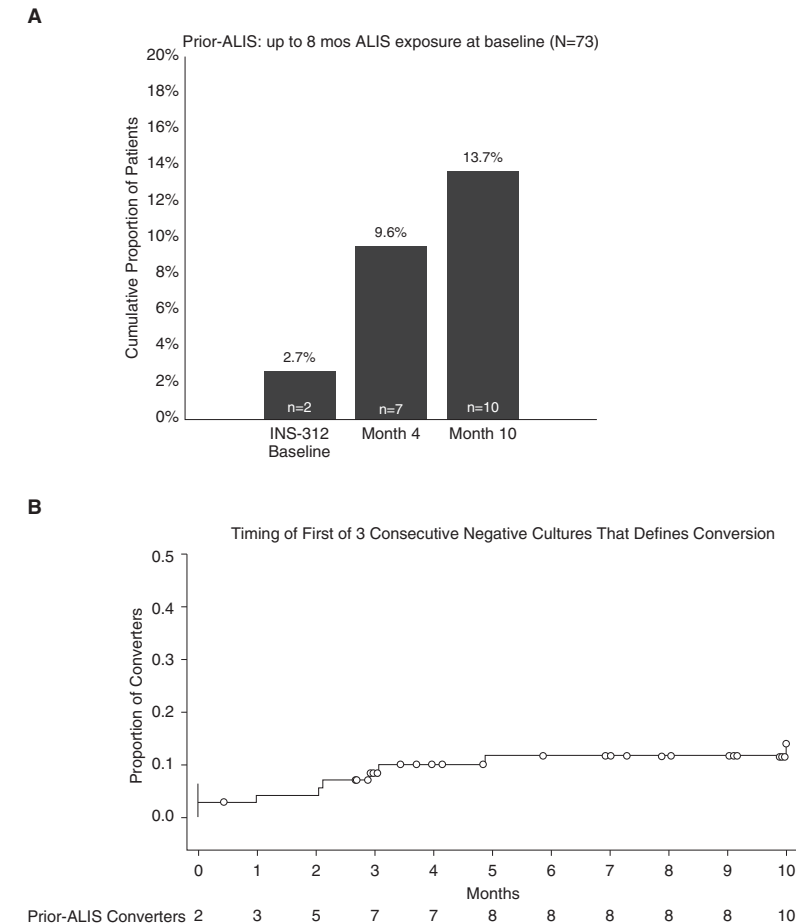
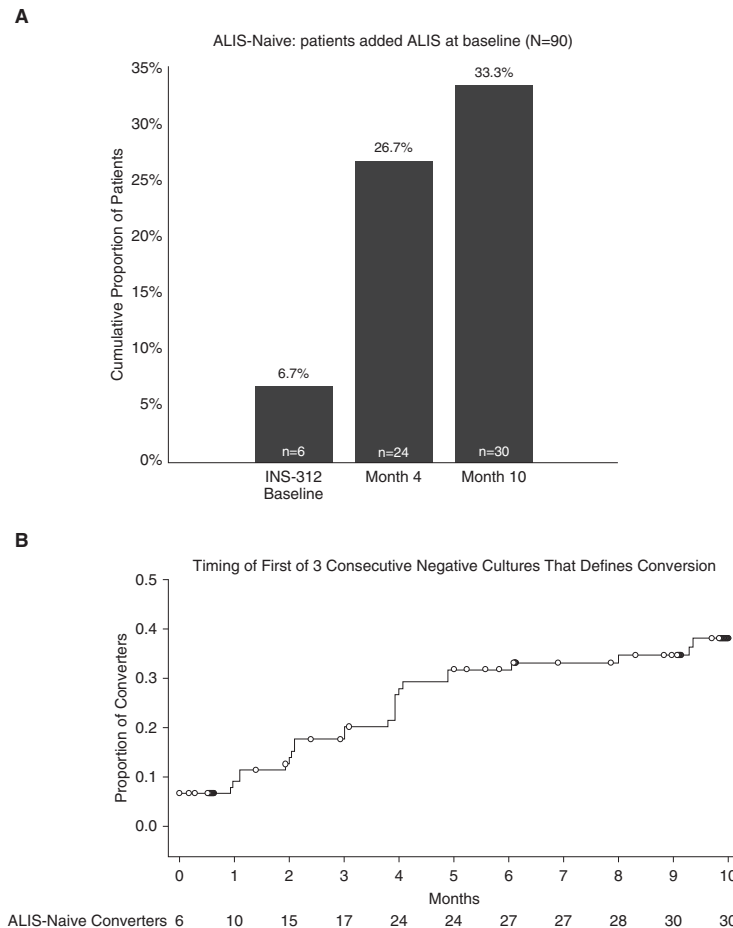
Parameter	ALIS-Naïve Cohort (N = 90)
Any TEAE	90 (100)
Grade 1: mild	21 (23.3)
Grade 2: moderate	33 (36.7)
Grade 3: severe	29 (32.2)
Grade 4: life threatening	3 (3.3)
Grade 5: death	4 (4.4)
TEAE in ≥10% of patients	
Dysphonia	39 (43.3)
Cough	32 (35.6)
Dyspnea	16 (17.8)
Fatigue	13 (14.4)
Hemoptysis	11 (12.2)
Infective exacerbation of bronchiectasis	11 (12.2)
Nausea	9 (10.0)
Diarrhea	9 (10.0)
TEAE: pulmonary exacerbation*	29 (32.2)
TEAE leading to discontinuation of ALIS	22 (24.4)
TEAE leading to discontinuation of GBT	8 (8.9)
TEAE leading to discontinuation of ALIS and GBT	5 (5.6)
TEAE leading to death	4 (4.4)
COPD exacerbation	1 (1.1)
Acute respiratory failure†	1 (1.1)
Pneumothorax	1 (1.1)
Pulmonary fibrosis progression‡	1 (1.1)
Any serious TEAE§	32 (35.6)
Serious TEAE occurring in ≥3% of patients	
MAC infection worsening or progression	5 (5.6)
Pneumonia	4 (4.4)
COPD exacerbation	4 (4.4)
Infective exacerbation of bronchiectasis	3 (3.3)
Serious TEAE: pulmonary exacerbation	17 (18.9)
Serious TEAE leading to discontinuation of ALIS	9 (10.0)
Respiratory TEAEs of special interest	
Bronchospasm	
Dyspnea	16 (17.8)
Wheezing	5 (5.6)
Bronchospasm	2 (2.2)
Dyspnea exertional	2 (2.2)
Infective exacerbation of underlying disease	
Infective exacerbation of bronchiectasis	11 (12.2)
COPD exacerbation	6 (6.7)
Hemoptysis	
Hemoptysis	11 (12.2)
Allergic alveolitis	
Interstitial lung disease	1 (1.1)
TEAEs of special interest typically associated with parenteral amikacin	
Ototoxicity	
Hearing loss¶	7 (7.8)
Tinnitus	6 (6.7)
Dizziness	5 (5.6)
Vertigo	2 (2.2)
Balance disorder	1 (1.1)
Nephrotoxicity	
Hematuria	5 (5.6)
Renal impairment	3 (3.3)
Blood creatinine increased	2 (2.2)
Leukocyturia	1 (1.1)
Proteinuria	1 (1.1)
Neuromuscular disorders	
Peripheral neuropathy	1 (1.1)
Balance disorder	1 (1.1)

Table 3. Prior-ALIS cohort: safety profile among patients with up to 8 months of ALIS exposure at baseline (safety population)

Parameter	Prior-ALIS Cohort (N = 73)
Any TEAE	68 (93.2)
Grade 1: mild	22 (30.1)
Grade 2: moderate	30 (41.1)
Grade 3: severe	13 (17.8)
Grade 4: life threatening	1 (1.4)
Grade 5: death	2 (2.7)
TEAE in ≥10% of patients	
Hemoptysis	11 (15.1)
Nasopharyngitis	10 (13.7)
Cough	9 (12.3)
Dyspnea	9 (12.3)
TEAE: pulmonary exacerbation*	22 (30.1)
TEAE leading to discontinuation of ALIS	6 (8.2)
TEAE leading to discontinuation of GBT	4 (5.5)
TEAE leading to discontinuation of ALIS and GBT	1 (1.4)
TEAE leading to death	2 (2.7)
COPD exacerbation	1 (1.4)
Lower respiratory tract infection	1 (1.4)
Any serious TEAE†	20 (27.4)
Serious TEAE occurring in ≥3% of patients	
Pneumonia	3 (4.1)
Serious TEAE: pulmonary exacerbation	7 (9.6)
Serious TEAE leading to discontinuation of ALIS	3 (4.1)
Respiratory TEAEs of special interest	
Bronchospasm	
Dyspnea	9 (12.3)
Wheezing	1 (1.4)
Infective exacerbation of underlying disease	
Infective exacerbation of bronchiectasis	7 (9.6)
COPD exacerbation	4 (5.5)
Hemoptysis	
Hemoptysis	11 (15.1)
Allergic alveolitis	
Alveolitis allergic	2 (2.7)
TEAEs of special interest typically associated with parenteral amikacin	
Ototoxicity	
Hearing loss‡	7 (9.6)
Dizziness	2 (2.7)
Tinnitus	1 (1.4)
Nephrotoxicity	
Hematuria	4 (5.5)
GFR decreased	2 (2.7)
Leukocyturia	1 (1.4)
Proteinuria	1 (1.4)
Azotemia	1 (1.4)
Renal failure	1 (1.4)
Neuromuscular disorders	
Peripheral neuropathy	1 (1.4)

Amikacin Liposome Inhalation Suspension

A 12-Month Open-Label Extension Clinical Trial



Inhaled Amikacin for Mabs

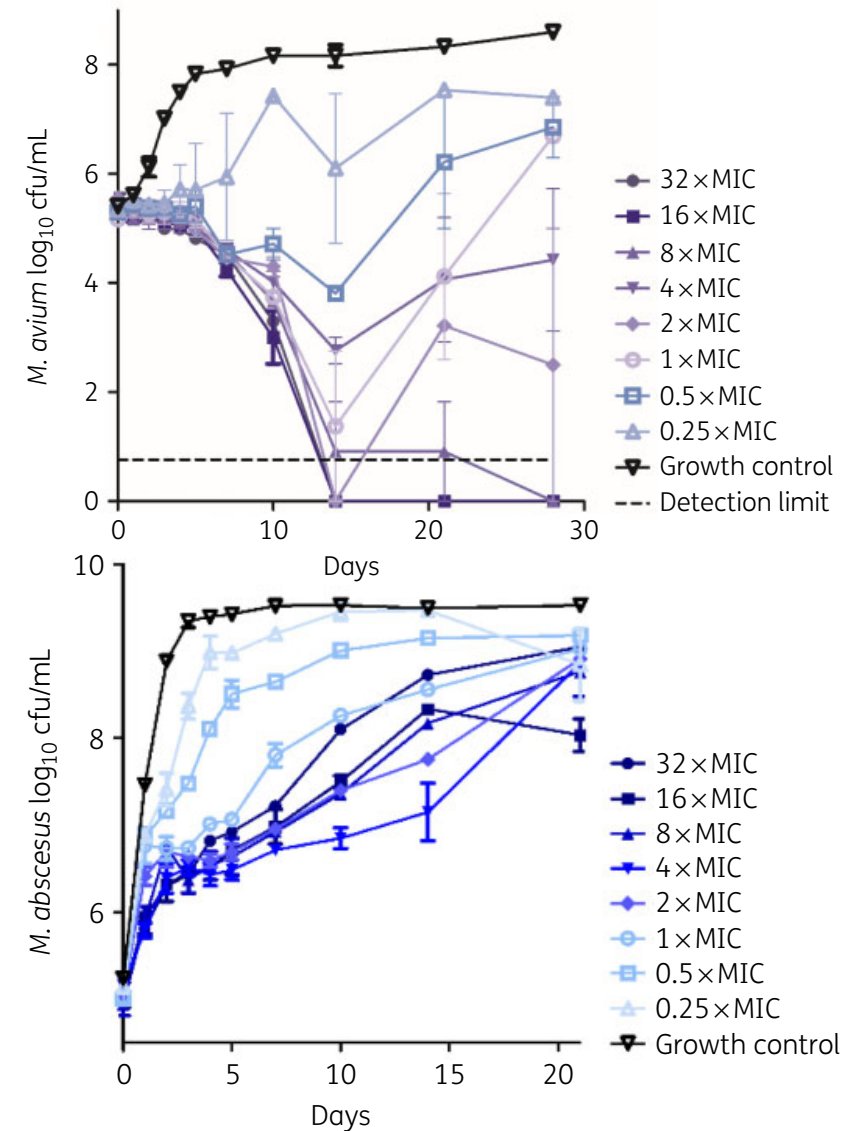
- 82 TT naïve patients with Mabs, 2015-2018
- During the initial phase, all patients received IV amikacin, imipenem (or ceftazidime), and oral azithromycin.
- Oral clofazimine was added in cases of *M abscessus subspecies abscessus* or *M abscessus subspecies massiliense* with cavitory lesions.
- During the continuation phase, amikacin was changed from an injectional to inhalational form.

TABLE 3] Treatment Outcome 12 Months After Initiation of Treatment

Outcome	Total (N = 82)	<i>M massiliense</i> (n = 46)	<i>M abscessus</i> (n = 36)	P Value
Symptomatic response				.047
Improved	72 (88)	44 (96)	28 (78)	
Unchanged	4 (5)	1 (2)	3 (8)	
Worsened	6 (7)	1 (2)	5 (14)	
Radiographic response on CT scan				.002
Improved	64 (78)	42 (93)	22 (61)	
Unchanged	7 (9)	3 (7)	4 (11)	
Worsened	11 (13)	1 (2)	10 (28)	
Culture conversion ^a	56 (68)	44 (96)	12 (33)	< .001
Time to conversion, mo	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-8.1)	.527
Microbiologic cure ^b	55 (67)	44 (96)	11 (31)	< .001
Cure ^c	53 (65)	42 (91)	11 (31)	< .001
Clinical cure ^d	6 (7)	0 (0)	6 (17)	< .001

Tedizolid

- **Linezolid** associato a scarsa tollerabilità → 45% eventi avversi (NTM)
 - 24% neuropatia periferica, 9% intolleranza GI, 8% anemia, 6% PLTpenia
- **Tedizolid**
 - 200 mg QD
 - Migliore tollerabilità e minore incidenza sindrome serotoninergica
 - Migliore penetrazione nell'ELF
 - Maggiore attività *in vitro*
 - Buone MIC per NTM (lievemente peggiori per *abscessus*)



Tedizolid



Prolonged tedizolid use in cutaneous non-tuberculous mycobacterial infection

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ARTICLE INFO

Keywords:

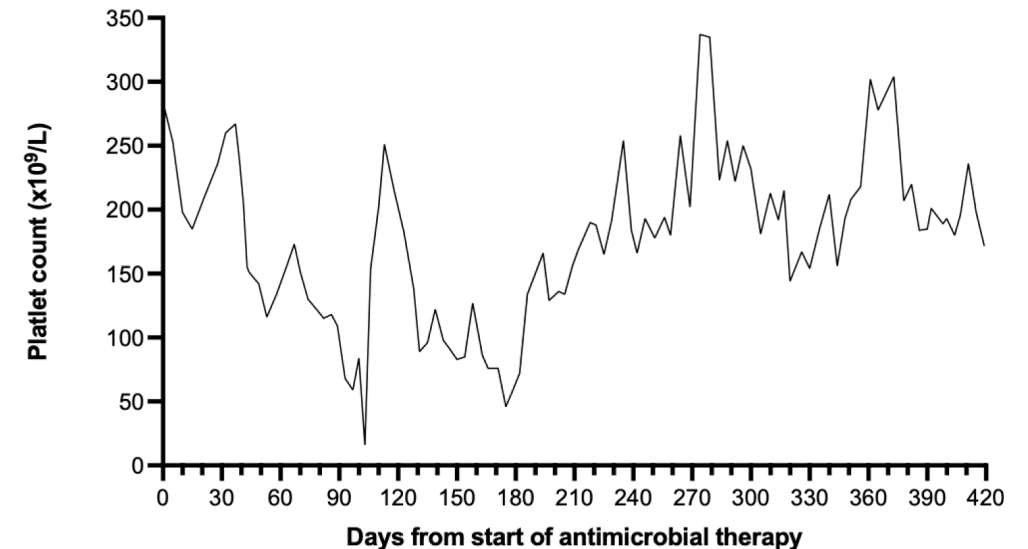
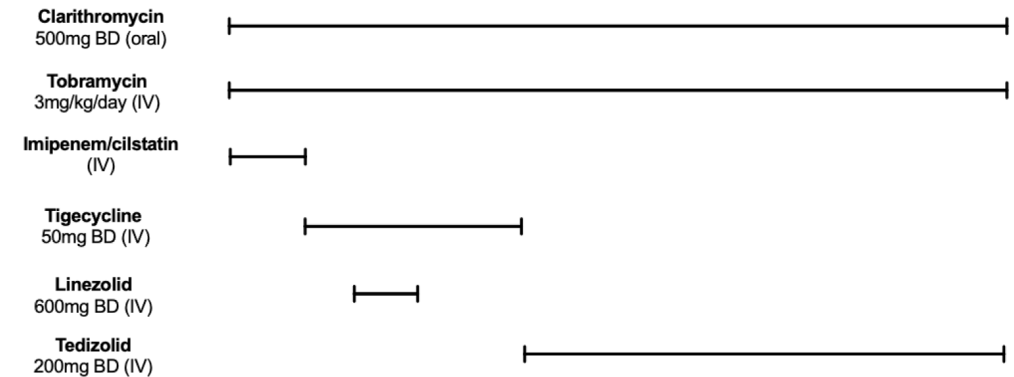
Non-tuberculous mycobacteria
Mycobacterium chelonae
Extrapulmonary infection
Tedizolid

ABSTRACT

Cutaneous non-tuberculous mycobacterial (NTM) infections are an emerging infectious disease and require a protracted course of combination antibiotics. Antimicrobial choice is limited by resistance and toxicity. Tedizolid is a new oxazolidinone antibiotic with *in vitro* activity against some NTM, but its use in the management of extrapulmonary NTM has not been described. We report on the utility of prolonged tedizolid use (8 months), after linezolid intolerance, in combination therapy in a case of difficult *Mycobacterium chelonae* cutaneous infection. Although tedizolid contributed to clinical remission, it may have also contributed to a multifocal peripheral neuropathy. Its efficacy may also have been limited by continued immunosuppression, with evidence to suggest disease relapse or treatment failure after completion of combination therapy. Tedizolid can be considered, with caution, in combination therapy for difficult cases of cutaneous NTM infection.

- Skin lesions from *M. chelonae* in a patient treated with mycophenolate (after steroids)

- MOX R, TMP/SFX R, DOX R, AMK I, LZD I
- severe thrombocytopenia with LZD
- irreversible bilateral sensorineural hearing loss and peripheral neuropathy (with neuropathic pain in both feet)



Tedizolid vs. Linezolid in SOT recipients

- Single-center, retrospective, US, 2010-2019
- 24 patients: 15 TDZ vs. LZD
- Mabs (1 *M. chelonae*)
- **No differences** were identified comparing the effects of tedizolid vs linezolid on platelet counts, absolute neutrophil counts (ANCs), and hemoglobin over 7 weeks using mixed-effects analysis of variance models.
 - ANC was significantly decreased in both groups after 7 weeks of therapy ($P = .04$).
- Approximately **20%** of patients in each arm **discontinued therapy** due to an ADE (no peripheral neuropathy)
- Seven of 12 (58%) and 2 of 3 (67%) patients were cured or clinically cured with TDZ- and LZD-containing regimens, respectively.

Bedaquilina

In Vitro Activity of Bedaquiline and Delamanid against Nontuberculous Mycobacteria, Including Macrolide-Resistant Clinical Isolates

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ABSTRACT We evaluated the *in vitro* activities of the antimicrobial drugs bedaquiline and delamanid against the major pathogenic nontuberculous mycobacteria (NTM). Delamanid showed high MIC values for all NTM except *Mycobacterium kansasii*. However, bedaquiline showed low MIC values for the major pathogenic NTM, including *Mycobacterium avium* complex, *Mycobacterium abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. kansasii*. Bedaquiline also had low MIC values with macrolide-resistant NTM strains and warrants further investigation as a potential antibiotic for NTM treatment.

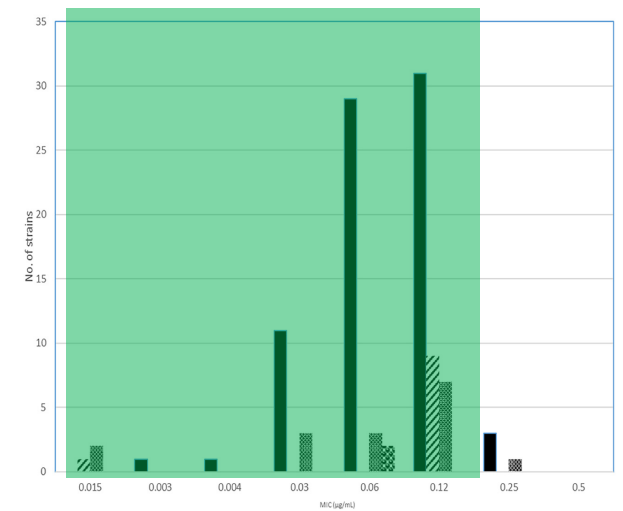
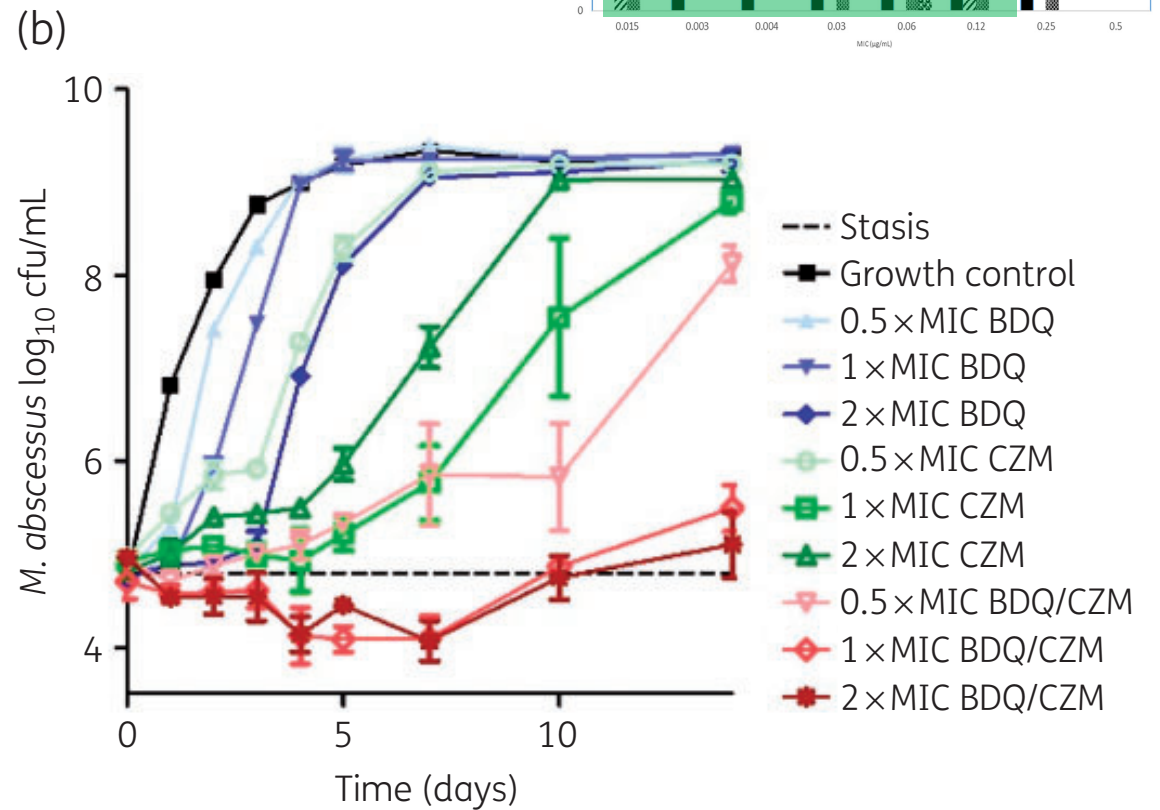
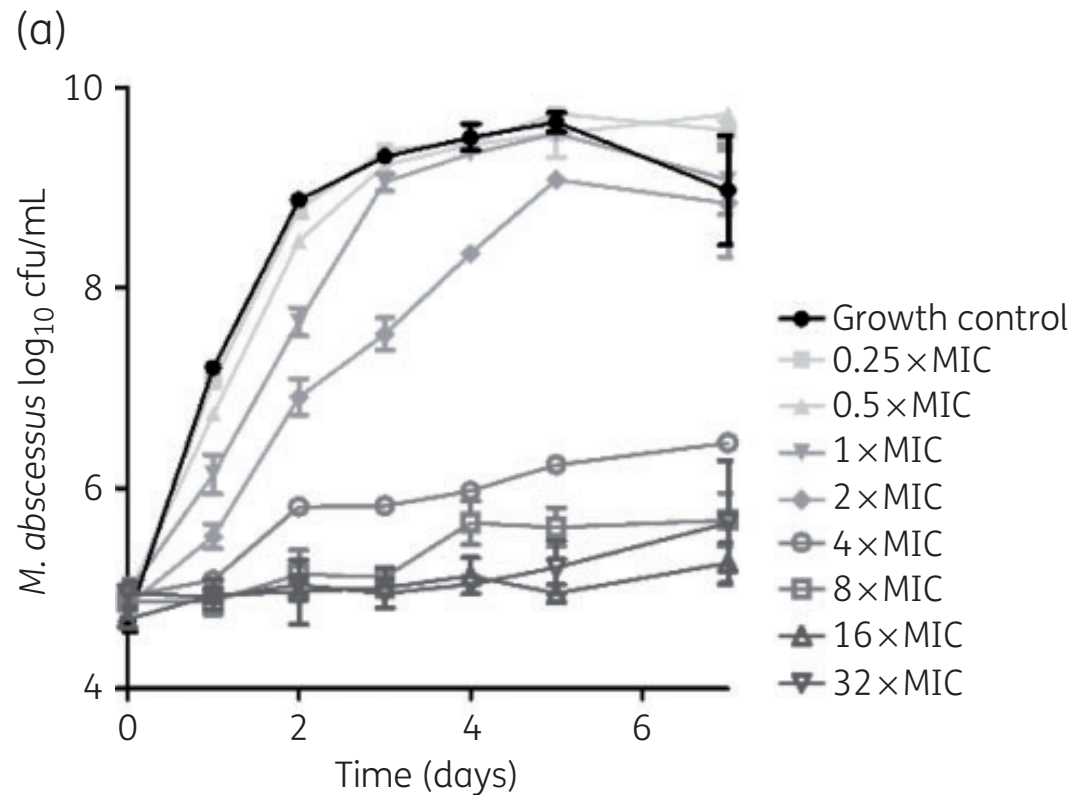
In Vitro Activity of Bedaquiline against Nontuberculous Mycobacteria in China

 Yu Pang,^a Huiwen Zheng,^b Yaoju Tan,^c Yuanyuan Song,^b Yanlin Zhao^b

National Clinical Laboratory on Tuberculosis, Beijing Key Laboratory on Drug-Resistant Tuberculosis Research, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Institute, Beijing, China^a; National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China^b; Department of Clinical Laboratory, Guangzhou Chest Hospital, Guangdong Province, Guangzhou, China^c

ABSTRACT The main goal of our study was to evaluate the *in vitro* bedaquiline susceptibility of six prevalent species of pathogenic nontuberculous mycobacteria (NTM) in China. In addition, we investigated the potential molecular mechanisms contributing to bedaquiline resistance in the different NTM species. Among slowly growing mycobacteria (SGM), bedaquiline exhibited the highest activity against *Mycobacterium avium*; the MIC₅₀ and MIC₉₀ values were 0.03 and 16 mg/liter, respectively. Among rapidly growing mycobacteria (RGM), *Mycobacterium abscessus* subsp. *abscessus* (*M. abscessus*) and *Mycobacterium abscessus* subsp. *massiliense* (*M. massiliense*) seemed more susceptible to bedaquiline than *Mycobacterium fortuitum*, with MIC₅₀ and MIC₉₀ values of 0.13 and >16 mg/liter, respectively, for both species. On the basis of bimodal distributions of bedaquiline MICs, we proposed the following epidemiological cutoff (ECOFF) values: 1.0 mg/liter for SGM and 2.0 mg/liter for RGM. Among *M. avium*, *Mycobacterium intracellulare*, *Mycobacterium kansasii*, *M. abscessus*, *M. massiliense*, and *M. fortuitum* isolates, 14 (29.8%), 41 (27.2%), 33 (39.3%), 44 (20.2%), 42 (25.8%), and 7 (31.8%), respectively, were resistant to bedaquiline. No significant differences in the proportions of bedaquiline resistance among these species were observed ($P > 0.05$). Genetic mutations were observed in 74 isolates (10.8%), with all nucleotide substitutions being synonymous. In conclusion, our data demonstrate that bedaquiline shows moderate *in vitro* activity against NTM species. Using the proposed ECOFF values, we could distinguish between bedaquiline-resistant and -susceptible strains with the broth dilution method. In addition, no nonsynonymous mutations in the *atpE* gene that conferred bedaquiline resistance in all six NTM species were identified.

Bedaquilina (2)



Bedaquiline

DISPATCHES

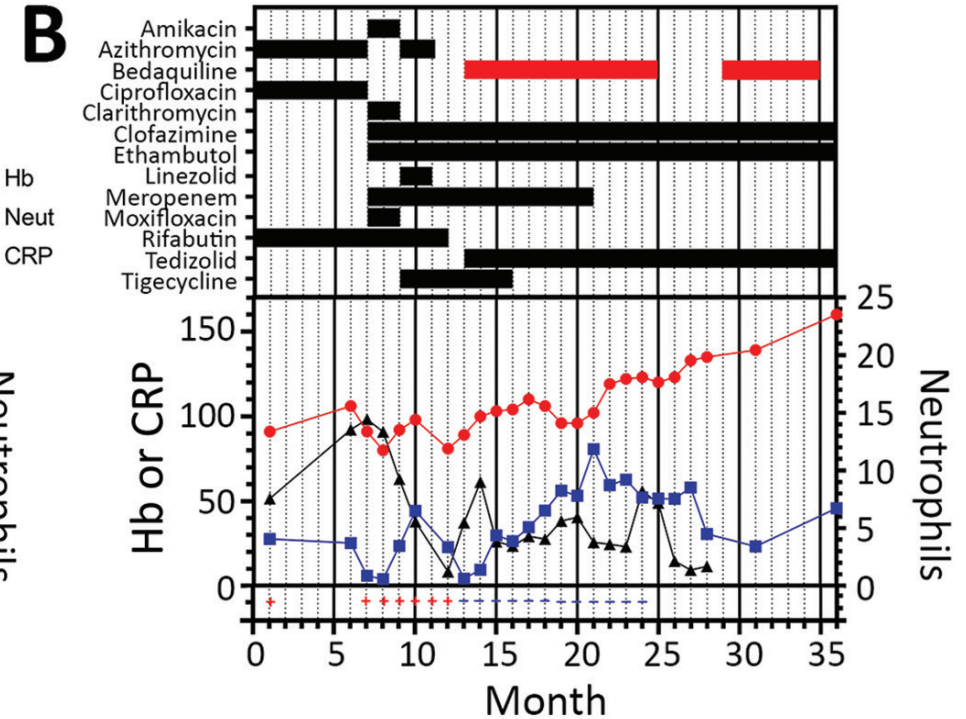
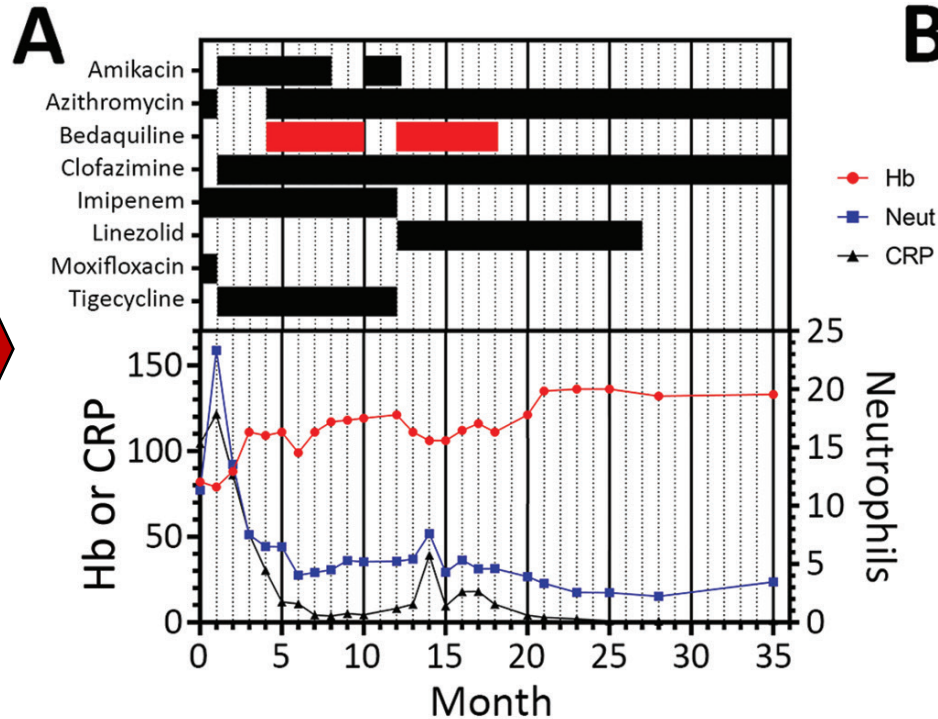
Bedaquiline as Treatment for Disseminated Nontuberculous *Mycobacteria* Infection in 2 Patients Co-Infected with HIV

Eliza Gil, Nicola Sweeney, Veronica Barrett, Stephen Morris-Jones, Robert F. Miller, Victoria J. Johnston, Michael Brown

AIDS with disseminated
MAC infection → poor
adherence → Macro-R

Colonic perforation
secondary to rectal trauma
→ emergency Hartmann's
procedure
→ 2 months later fevers,
breathlessness, and a
purulent exudate at the
abdominal wound site
→ Mabs

Well controlled HIV





Short communication

Efficacy and safety of tigecycline for *Mycobacterium abscessus* disease

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ARTICLE INFO

Keywords:

Nontuberculous mycobacteria

Mycobacterium abscessus

Tigecycline

Efficacy

Safety

ABSTRACT

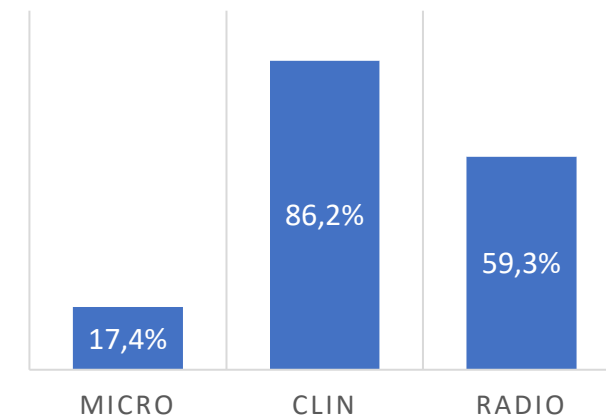
Purpose: *Mycobacterium abscessus* disease is one of the most difficult mycobacterial infections to cure, as the bacterium is highly resistant to conventional antibiotics. The purpose of this study was to evaluate the efficacy and safety of tigecycline treatment of *M. abscessus* disease.

Procedure: We performed retrospective chart reviews of patients with *M. abscessus* disease receiving tigecycline-containing regimens at National Jewish Health from January 2009 to December 2017.

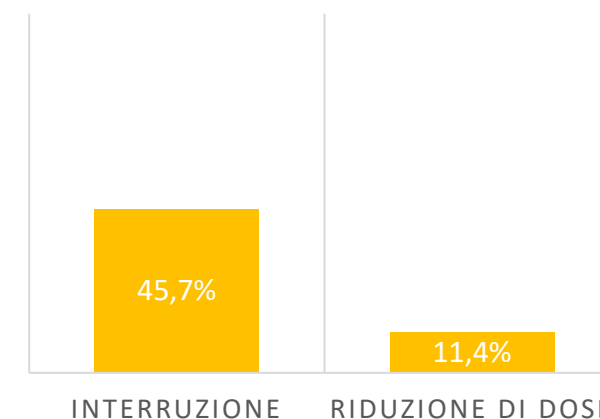
Main findings: Among the 35 patients, pulmonary disease was the most common presentation of *M. abscessus* disease (n = 29, 82.9%). Of those receiving tigecycline treatment, 17.4% (4/23) showed microbiological improvement (≥ 2 consecutive negative sputum cultures), while 86.2% (25/29) and 59.3% (16/27) showed symptomatic and radiological improvements, respectively. The rate of dose reduction or discontinuation of tigecycline owing to adverse drug reactions was 57.1% (20/35) at a median of 56.5 days (IQR 10.8–122.3). The most common adverse drug reactions were gastrointestinal side effects, including nausea, vomiting, and diarrhea.

Conclusions: Tigecycline-containing regimens for *M. abscessus* disease have a high rate of symptomatic and radiological improvement. However, considering the poor microbiological response and the common adverse effects, selection of patients for tigecycline treatment and monitoring for adverse drug reactions should be performed carefully.

MIGLIORAMENTO



TOLLERABILITÀ





Potency of Omadacycline against *Mycobacteroides abscessus* Clinical Isolates *In Vitro* and in a Mouse Model of Pulmonary Infection

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Emily C. Maggioncalda and Elizabeth Story-Roller contributed equally to this study. Author order was determined alphabetically.

ABSTRACT The incidence of nontuberculous mycobacterial diseases in the United States is rising and has surpassed that of tuberculosis. Most notable among the nontuberculous mycobacteria is *Mycobacteroides abscessus*, an emerging environmental opportunistic pathogen capable of causing chronic infections. *M. abscessus* disease is difficult to treat, and the current treatment recommendations include repurposed antibiotics, several of which are associated with undesirable side effects. In this study, we have evaluated the activity of omadacycline, a new tetracycline derivative, against *M. abscessus* using *in vitro* and *in vivo* approaches. Omadacycline exhibited an MIC₉₀ of 0.5 µg/mL against a panel of 32 contemporary *M. abscessus* clinical isolates, several of which were resistant to antibiotics that are commonly used for treatment of *M. abscessus* disease. Omadacycline combined with clarithromycin, azithromycin, cefdinir, rifabutin, or linezolid also exhibited synergism against several *M. abscessus* strains and did not exhibit antagonism when combined with an additional nine antibiotics also commonly considered to treat *M. abscessus* disease. Concentration-dependent activity of omadacycline was observed in time-kill assessments. Efficacy of omadacycline was evaluated in a mouse model of lung infection against four *M. abscessus* strains. A dose equivalent to the 300-mg standard oral human dose was used. Compared to the untreated control group, within 4 weeks of treatment, 1 to 3 log₁₀ fewer *M. abscessus* CFU were observed in the lungs of mice treated with omadacycline. Treatment outcome was biphasic, with bactericidal activity observed after the first 2 weeks of treatment against all four *M. abscessus* strains.

KEYWORDS omadacycline, *Mycobacterium abscessus*, pulmonary infection

Mycobacteroides abscessus (formerly *Mycobacterium abscessus*) (1) is an environmental nontuberculous mycobacterium (NTM) and a causative pathogen of pulmonary and soft tissue infections, among others. This organism has been described as a “clinical and antibiotic nightmare” (2, 3), as it demonstrates intrinsic resistance to a wide range of antibiotic classes (4, 5). As only a few oral antibiotics show activity against *M. abscessus*, the current treatment regimen, which requires regular and frequent administration of intravenous drugs is a logistical challenge for patients. Acquired resistance to important antibiotic classes, particularly macrolides and aminoglycosides, has further limited therapeutic options. Therefore, *M. abscessus* disease treatment is challenging, and there are currently no FDA approved treatment agents or regimens for this indication. Current treatment options include repurposed antibiotics and regimens developed on the basis of empirical evidence and consensus from experts (6–10). Cure rates using antibiotics alone are as low as 25 to 40% (11, 12).

M. abscessus is one of the most frequently recovered NTM from patients, causing ~10% of all NTM pulmonary infections (13). It was the second most common NTM

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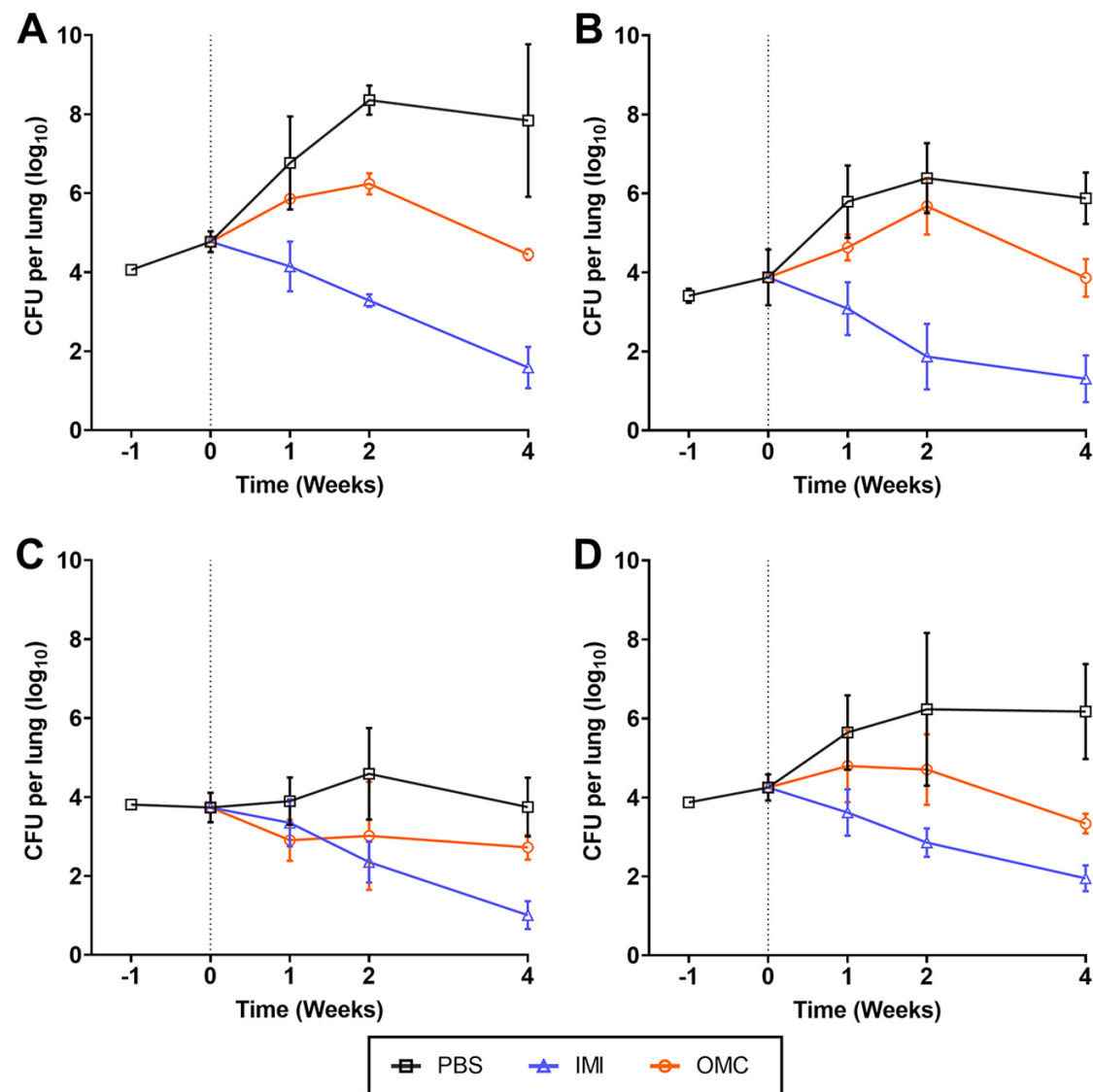
Received 26 August 2021

Returned for modification 10 September 2021

Accepted 14 October 2021

Accepted manuscript posted online 18 October 2021

Published 18 January 2022





Epetraborole Is Active against *Mycobacterium abscessus*

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ABSTRACT Benzoxaboroles are a new class of leucyl-tRNA synthetase inhibitors. We recently reported that the antitubercular 4-halogenated benzoxaboroles are active against *Mycobacterium abscessus*. Here, we find that the nonhalogenated benzoxaborole epetraborole, a clinical candidate developed for Gram-negative infections, is also active against *M. abscessus* *in vitro* and in a mouse model of infection. This expands the repertoire of advanced lead compounds for the discovery of a benzoxaborole-based candidate to treat *M. abscessus* lung disease.

KEYWORDS epetraborole, *Mycobacterium abscessus*, NTM, nontuberculous mycobacteria, benzoxaborole

Mycobacterium abscessus lung disease is notoriously difficult to treat due to the bacterium's high intrinsic drug resistance (1, 2). In addition to resistance to all first-line tuberculosis (TB) drugs, *M. abscessus* displays resistance to macrolides (3, 4), threatening the current macrolide-based treatment regimens (2, 5). Therefore, new antibiotics with novel targets and mechanisms of action are needed to treat this disease (6).

Benzoxaboroles are a class of boron-heterocyclic antimicrobials that target leucyl-tRNA synthetase (LeuRS) (7). Acting through the oxaborole tRNA-trapping (OBORT) mechanism (8), these compounds form adducts with uncharged tRNA^{Leu} molecules that subsequently bind to the LeuRS editing domain, blocking protein synthesis. Following the discovery of tavaborole (7, 8), a benzoxaborole with antifungal activity, this compound class was optimized for antibacterial activity. Addition of a 3-aminomethyl group to the benzoxaborole core improved interactions with the editing domain of *Escherichia coli* LeuRS, while a 7-*O*-propanol substituent added a novel interaction with the phosphate backbone of tRNA^{Leu} (9). Combining these modifications yielded epetraborole (Fig. 1), a clinical candidate with potent activity against a broad range of Gram-negative bacteria (9, 10). The subsequent addition of a 4-halogen group (particularly Cl or Br) improved antituberculosis activity (11–13).

Recently, we reported that the antituberculosis 4-halogen benzoxaborole EC/11770 (Fig. 1) is active against *M. abscessus* *in vitro* and *in vivo* in a mouse infection model (14). Here, we asked whether the anti-Gram-negative, nonhalogenated benzoxaborole epetraborole (Fig. 1) is active against *M. abscessus*. We first measured the MIC of this compound against our screening strain *M. abscessus* subsp. *abscessus* Bamboo (15) in Middlebrook 7H9 medium using 96-well plates, as previously described (14). Surprisingly, epetraborole retained activity against culture collection reference strains for each of the three subspecies of the *M. abscessus* complex and a panel of *M. abscessus* clinical isolates (16, 17) (Table 1). Taken together, the anti-Gram-negative, nonhalogenated benzoxaborole epetraborole was active against the *M. abscessus* complex *in vitro*.

To confirm that epetraborole indeed exerts its antimycobacterial activity by targeting *M. abscessus* LeuRS, we selected for epetraborole-resistant *M. abscessus* mutants (Table 2).

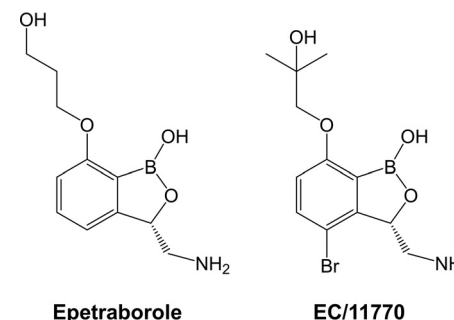


FIG 1 Structures of epetraborole and EC/11770.

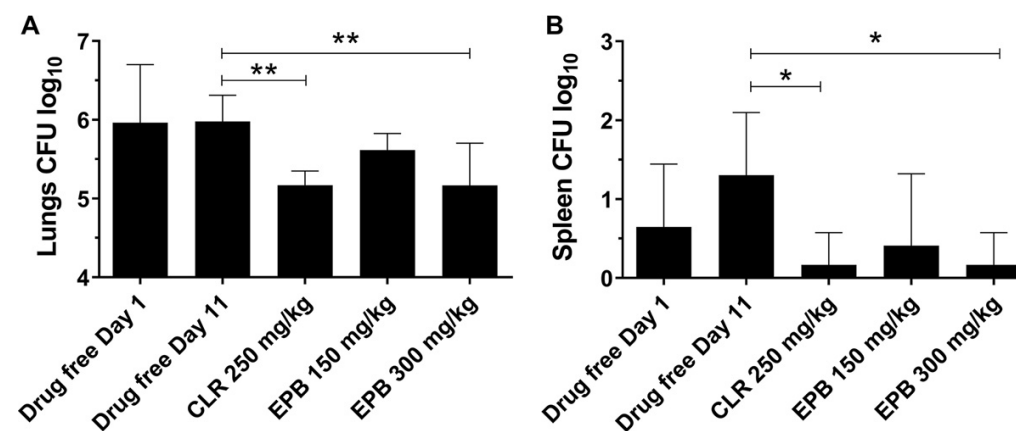


FIG 2 Epetraborole is active against *M. abscessus* *in vivo*. Lung CFU (A) and spleen CFU (B) from NOD SCID mice 1 day after intranasal infection with *Mab* (drug-free day 1) and following daily oral administration of drug-free vehicle, clarithromycin (CLR), or epetraborole (EPB) for 10 days (day 11). Data represent the means plus standard deviations from six mice per treatment group. Statistical significance of the results was analyzed by one-way analysis of variance (ANOVA) multiple-comparison and Tukey's posttests. *, $P < 0.05$; **, $P < 0.01$.

Citation Ganapathy US, Gengenbacher M, Dick T. 2021. Epetraborole is active against *Mycobacterium abscessus*. Antimicrob Agents Chemother 65:e01156-21. <https://doi.org/10.1128/AAC.01156-21>.

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Received 7 June 2021

Returned for modification 30 June 2021

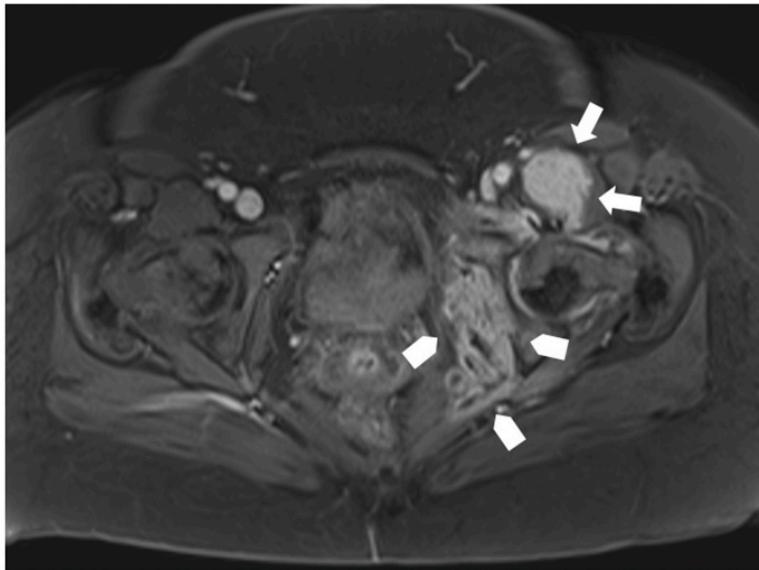
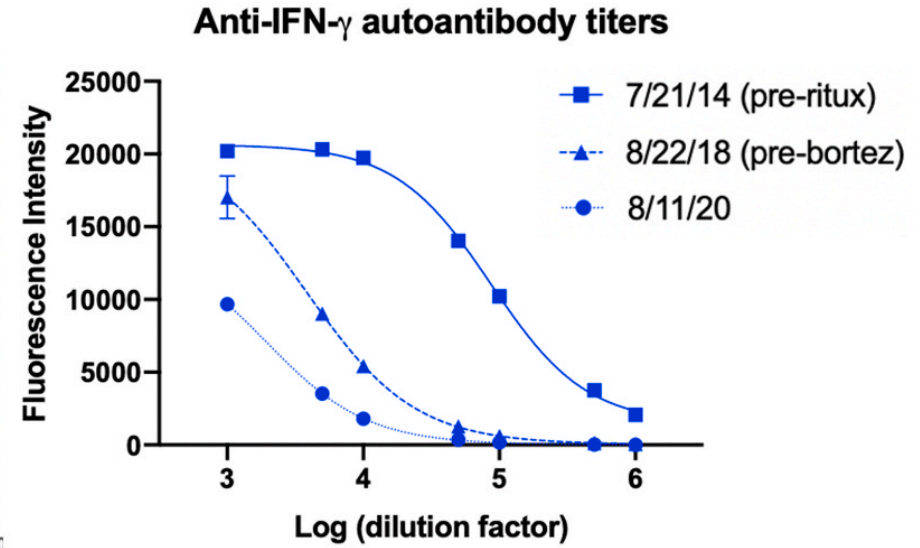
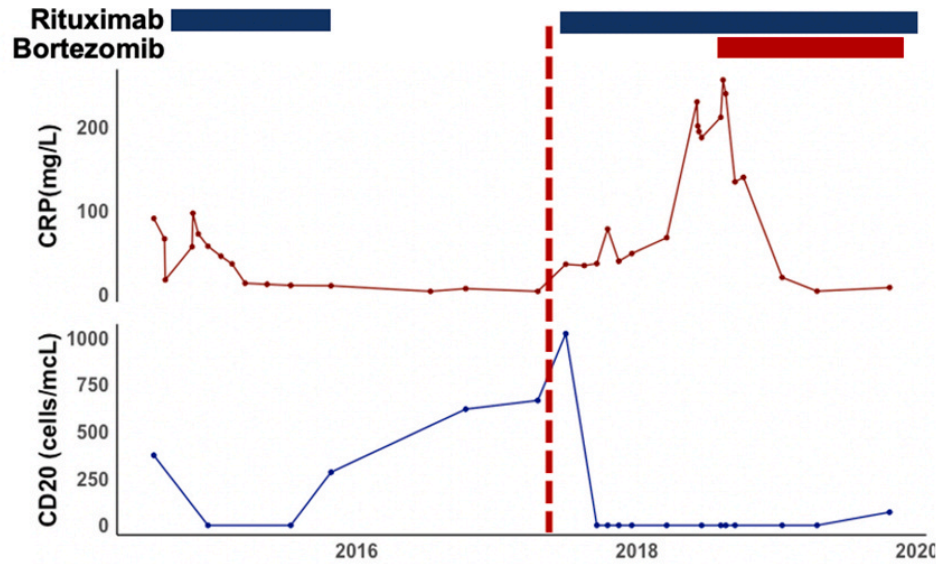
Accepted 13 July 2021

Accepted manuscript posted online 19 July 2021

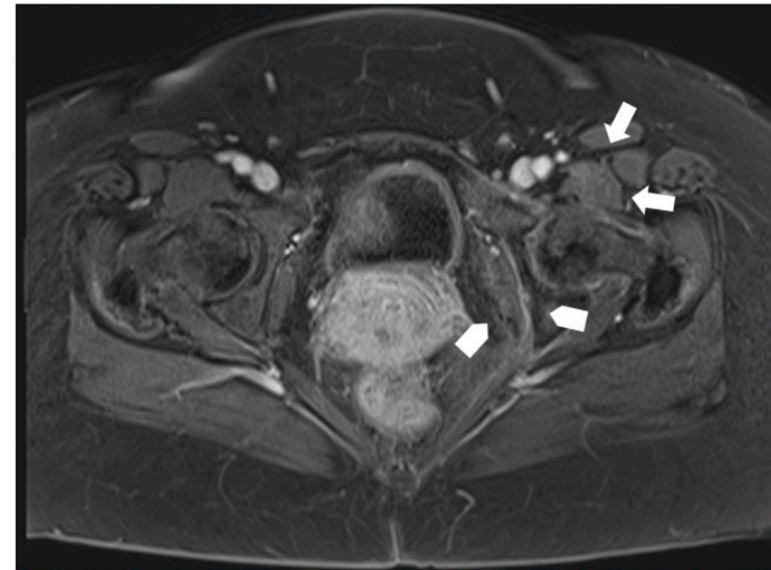
Published 17 September 2021

Disseminated NTM infections in patients with anti-IFN gamma autoantibodies – treatment?

- Recent evidence has supported the use of rituximab in the management of patients with anti-IFN γ autoantibodies and disseminated opportunistic infections.
 - Rituximab decreases autoantibody titers, which improves IFN γ signaling, leading to better clinical outcomes.
 - Serum anti-IFN γ autoantibody titers often correlate with disease activity.
- Progressive infection despite improvement in titers has also been described:
 - Long-lived autoantibody producing plasma cells which are not targeted by CD20+ B-cell depletion?
 - **Case report of bortezomib (proteasome inhibitor, used in multiple myeloma and mantle cell lymphoma)**



Pre-bortezomib



Post-bortezomib

Pharmacology

Low PK targets in antiNTM treatment

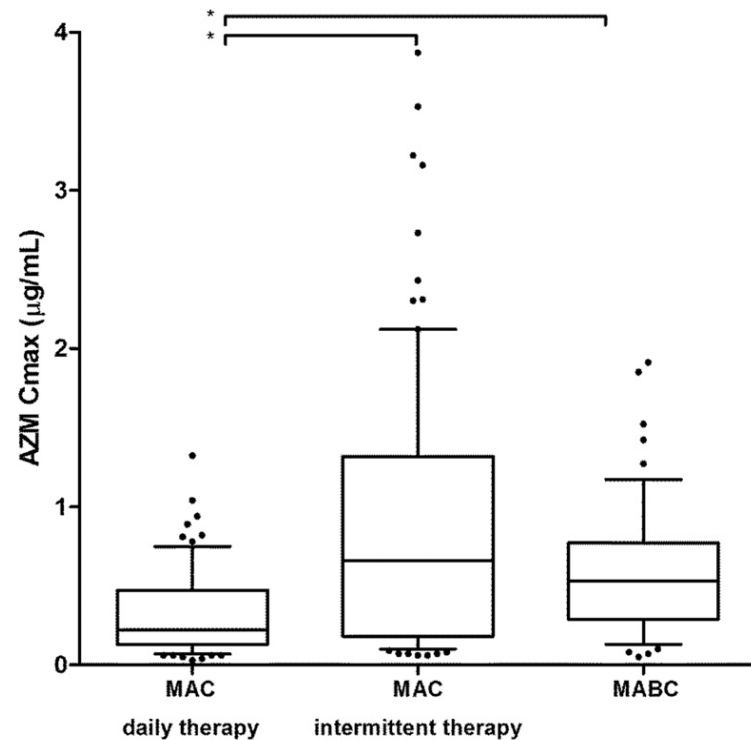
TABLE 4. RESULTS OF PHARMACOKINETIC ANALYSES OF KEY ANTIMYCOBACTERIAL DRUGS

Drug	N	Mean Daily Dose (mg/kg)	C _{max} ± SD	C _{last} ± SD	% Low @ C _{max} (n)	Mean AUC _{0-6/7} ± SD
Rifampicin	326	9.62 ± 1.63	18.76 ± 6.61	6.20 ± 3.13	5% (17)	68.42 ± 24.26
Ethambutol	431	17.65 ± 3.52	2.27 ± 1.01	1.16 ± 0.51	48% (207)	10.18 ± 4.35
Clarithromycin	59	14.33 ± 5.09	2.31 ± 1.89	1.32 ± 1.51	56% (33)	10.67 ± 9.53
Azithromycin	367	6.71 ± 2.48	0.33 ± 0.23	0.18 ± 0.13	35% (129)	1.47 ± 1.00
Moxifloxacin	96	6.73 ± 1.60	4.42 ± 1.46	2.86 ± 1.05	13% (12)	18.81 ± 6.46
Ciprofloxacin	17	12.04 ± 4.08	3.60 ± 2.04	1.41 ± 0.78	76% (13)	13.61 ± 7.58
Amikacin	113	15.05 ± 3.62	55.30 ± 16.88*	12.34 ± 6.42	n.a.	152.82 ± 50.83*
Clofazimine	17	1.62 ± 0.28	0.43 ± 0.19	0.44 ± 0.19	53% (9)	2.25 ± 0.96
Rifabutin	51	4.80 ± 1.46	0.52 ± 0.29	0.28 ± 0.19	27% (14)	2.28 ± 1.31

Definition of abbreviations: AUC = area under the concentration time curve; C_{last} = final concentrations; C_{max} = maximum observed concentration; n.a. = not applicable.

* After backcalculation for C_{max} (see METHODS).

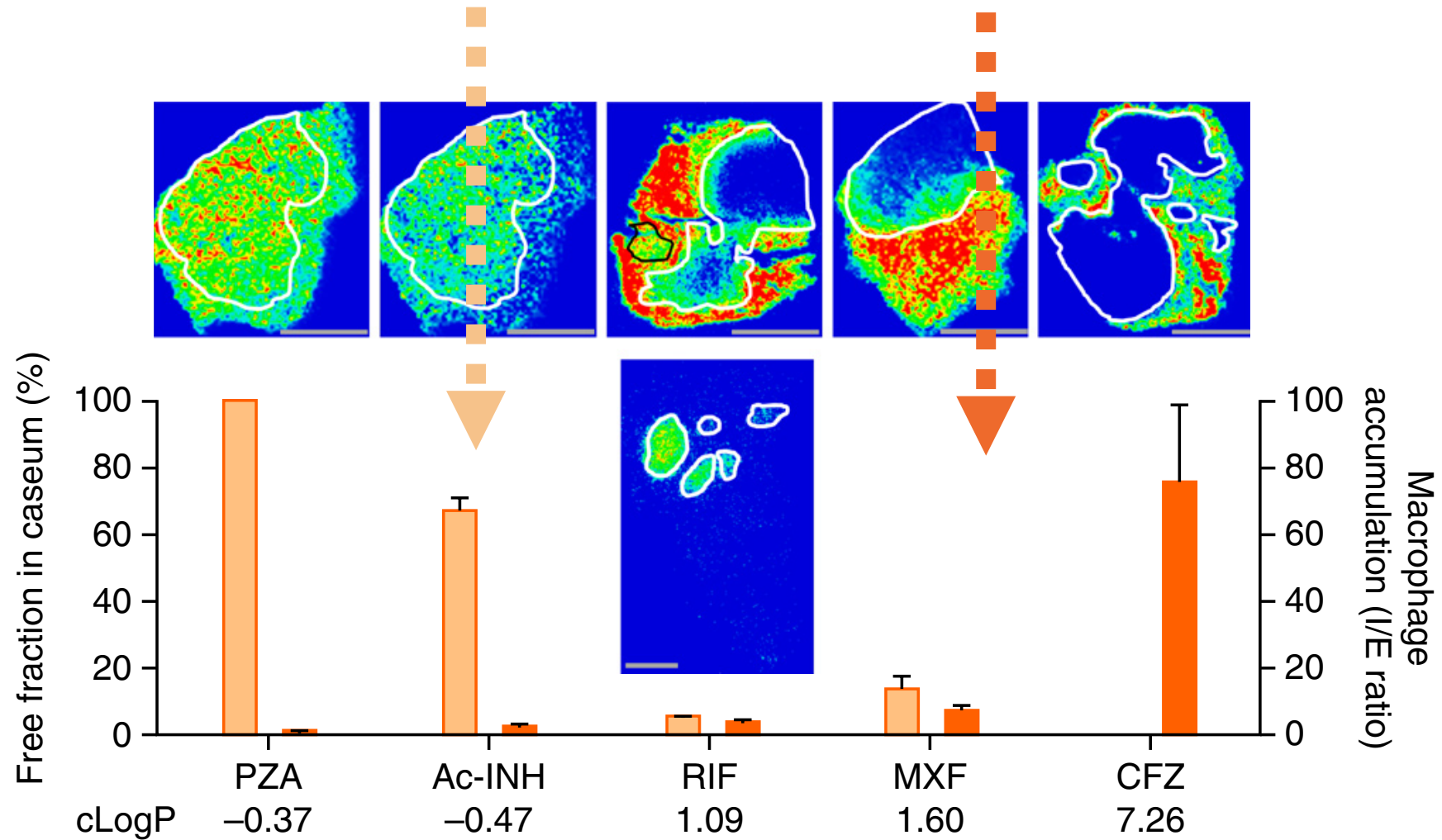
AZT Cmax and Treatment outcome



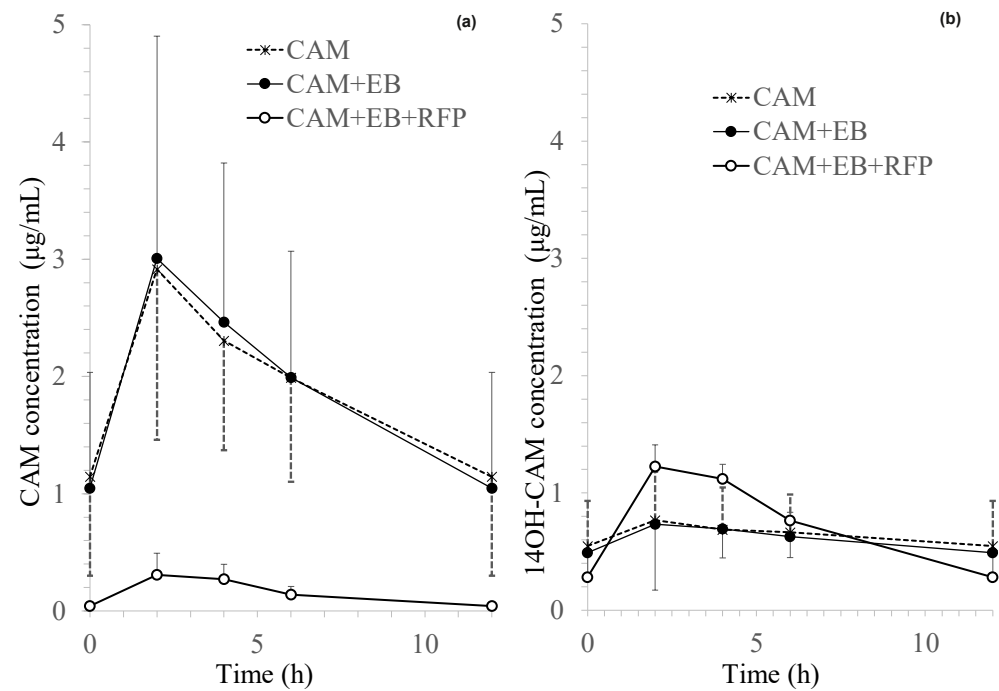
AZM Cmax (µg/mL) [†]	0.22 (0.13-0.47)	0.66 (0.18-1.32)	0.53 (0.29-0.77)
AZM Cmax < 0.2 µg/mL	36/77 (46.8%)	23/89 (25.8%)	9/55 (16.4%)

Therapy type	C _{max} (µg/ml) by drug ^b	Favorable responses	Unfavorable responses	Univariate analysis		Multiple logistic regression ^c	
				OR (95% CI)	P	aOR (95% CI)	P
Daily	AZM	0.24 (0.14–0.51)	0.18 (0.08–0.35)	1.53 (1.01–2.31)	0.045	1.58 (1.01–2.48)	0.044
	AZM ≥0.2	29/52 (55.8)	12/25 (48.0)	1.37 (0.53–3.56)	0.523	1.45 (0.52–4.04)	0.476
	AZM ≥0.4	21/52 (40.4)	4/25 (16.0)	3.56 (1.07–11.86)	0.039	3.98 (1.06–14.85)	0.040
	RIF ^d	11.2 (7.4–15.1)	13.7 (8.3–20.4)	0.92 (0.64–1.34)	0.678	1.00 (0.66–1.52)	0.989
	RIF ≥8.0	36/52 (69.2)	20/25 (80.0)	0.56 (0.18–1.76)	0.324	0.68 (0.19–2.38)	0.545
	EMB ^d	3.4 (1.8–4.6)	2.4 (1.7–3.5)	1.34 (0.79–2.25)	0.279	1.30 (0.73–2.31)	0.367
Intermittent	EMB ≥2.0	37/52 (71.2)	17/25 (68.0)	1.16 (0.41–3.26)	0.777	1.14 (0.38–3.46)	0.810
	AZM ^d	0.65 (0.18–1.31)	1.00 (0.18–1.44)	0.84 (0.59–1.19)	0.322	0.85 (0.58–1.23)	0.379
	AZM ≥0.2	54/73 (74.0)	12/16 (75.0)	0.95 (0.27–3.30)	0.932	1.01 (0.27–3.72)	0.991
	RIF ^d	11.2 (3.0–21.6)	12.0 (6.5–19.5)	0.87 (0.64–1.18)	0.382	0.93 (0.67–1.27)	0.636
	RIF ≥8.0	47/73 (64.4)	11/16 (68.8)	0.82 (0.26–2.62)	0.740	1.12 (0.33–3.84)	0.861
	EMB ^{d,e}	3.5 (2.0–5.6)	4.8 (3.0–6.6)	0.65 (0.35–1.21)	0.177	0.63 (0.33–1.23)	0.176
	EMB ≥2.0	55/72 (76.4)	14/16 (87.5)	0.46 (0.10–2.24)	0.338	0.41 (0.08–2.13)	0.291

PK TISSUTALE: caseum vs. macrofagi



The effect of RIF on CAM/14-OH-CAM



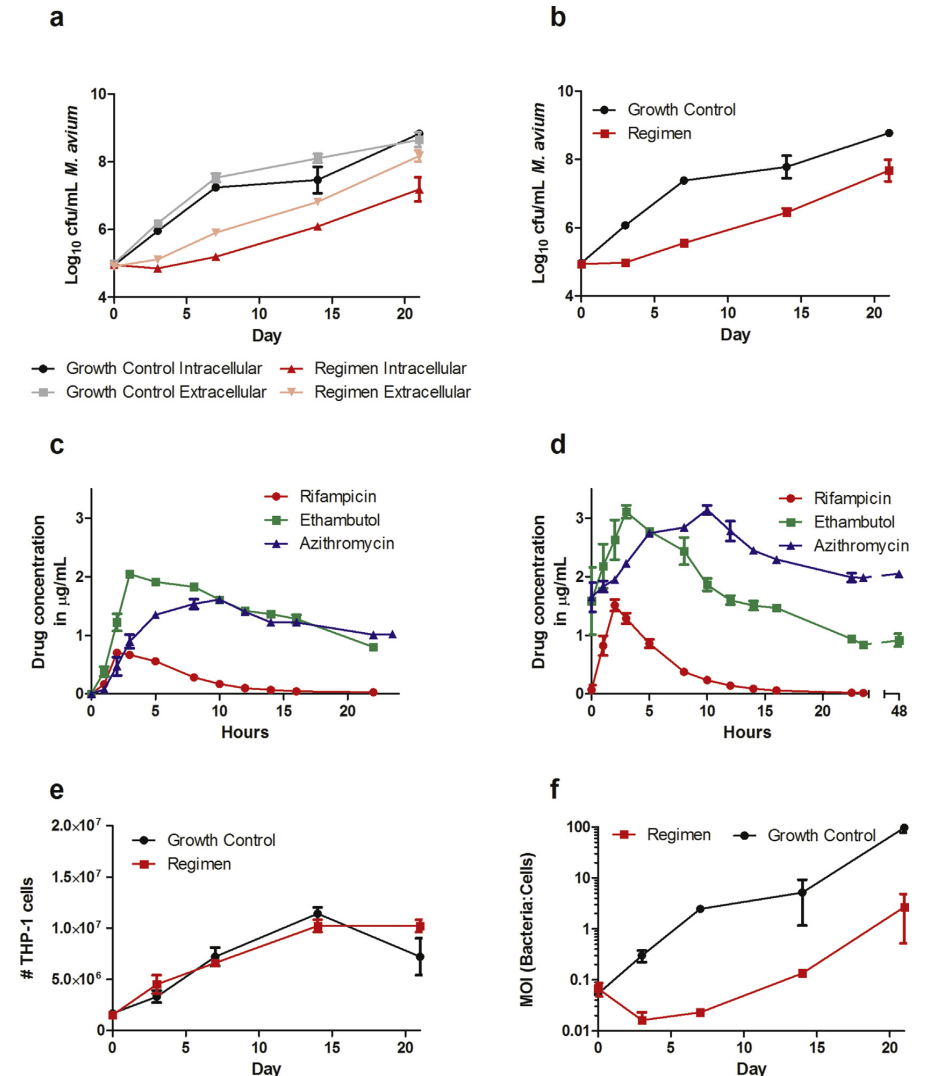
Pharmacokinetic parameters of CAM and 14-OH CAM in CAM monotherapy and in CAM+EB and CAM+EB+RFP combination therapy in patients with *Mycobacterium avium* complex lung disease.

	CAM				14-OH CAM			
	CAM (n = 10)	CAM+EB (n = 10)	CAM+EB+RFP (n = 9)	P-value	CAM (n = 10)	CAM+EB (n = 10)	CAM+EB+RFP (n = 9)	P-value
AUC _{0-1last} (µg·h/mL)	21.5 (17.7–32.3)	19.9 (14.3–31.3)	1.7 (1.4–1.8)	0.000	8.2 (6.3–9.3)	8.2 (7.3–9.3)	9.1 (7.3–10.9)	0.633
AUC ratio (vs. CAM monotherapy)	–	0.93	0.08		–	1.00	1.11	
C _{max} (µg/mL)	3.1 (2.7–3.8)	2.9 (1.9–4.1)	0.4 (0.2–0.4)	0.000	0.8 (0.7–0.9)	0.9 (0.7–1)	1.5 (1.2–1.5)	0.008
T _{max} (h)	2 (2–2)	2 (2–2)	2 (2–4)	0.796	2 (2–2)	4 (2–4)	2 (2–4)	0.247
T _{1/2} (h)	5.9 (5.3–9.8)	7.1 (4–11.9)	2.8 (2–3.2)	0.005	16.2 (9.6–34.6)	17 (12–56.5)	3.1 (2.5–4.7)	0.000
CL (L/h)	18.6 (12.4–22.9)	20.1 (13–28)	235.3 (219.8–289.9)	0.000	49.3 (42.9–63.2)	48.7 (42.8–55)	43.9 (36.7–55.1)	0.633

^a AUC=area under the curve. ^b The value are medians (IQRs).

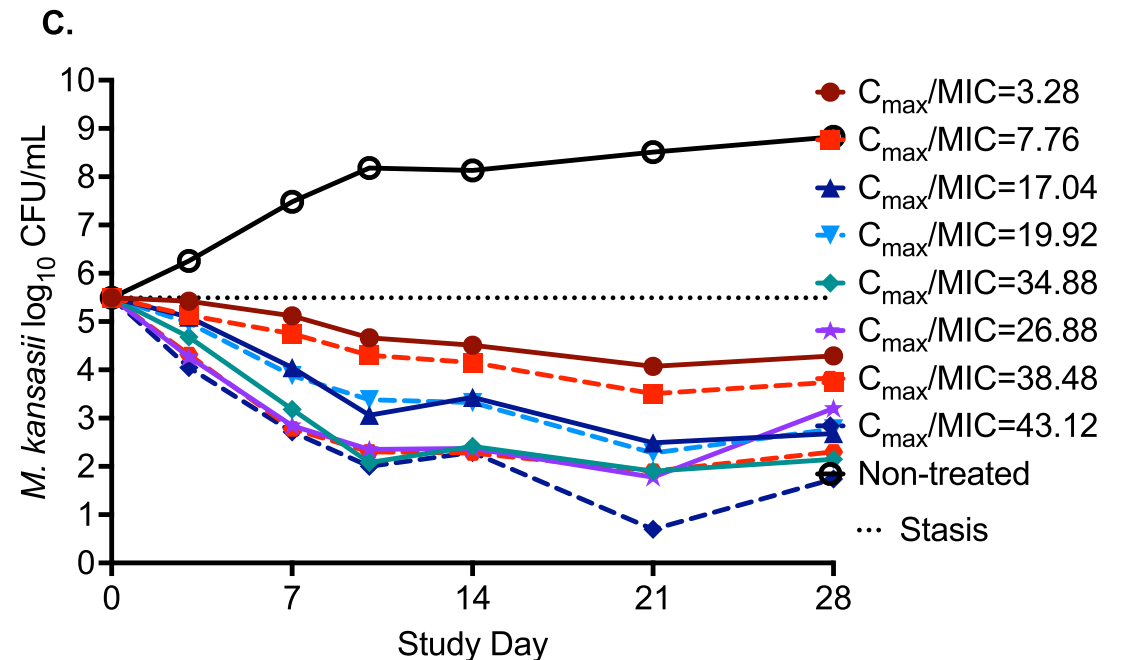
RIF/AZT/ETB for MAC – hollow fiber model

- PK simulation of AZT, ETB and RIF in plasma and epithelial lining fluid (ELF) in a HFS, exposing THP-1 cells infected with *M. avium* to the triple-drug regimen for 3 weeks.
 - We accounted for drug-drug interactions and protein-binding.
 - We differentiated the effects on the intracellular and extracellular mycobacterial population.
- We find that plasma drug concentrations fail to hold the MAC bacterial load static (DLog10 CFU/mL Control:Regimen 1/4 0.66 ± 0.76 and 0.45 ± 0.28 at 3 and 21 days); **ELF concentrations do hold the bacterial load static for 3 days and inhibit bacterial growth for the duration of the experiment** (DLog10 CFU/mL Control:Regimen 1/4 1.1 ± 0.1 and 1.64 ± 0.59 at 3 and 21 days).



RIF PK and *M. kansasii* – hollow fiber model

- We retrospectively collected clinical data from 33 patients with *M. kansasii* pulmonary disease to determine the time-to-sputum culture conversion (SCC) upon treatment with a standard combination regimen consist of isoniazid-rifampin-ethambutol.
- Next, MIC experiments with 20 clinical isolates were performed, followed by a dose-response study with the standard laboratory strain using the hollow-fiber system model of *M. kansasii* infection (HFS-Mkn).
- Finally, in silico clinical trial simulations were performed to determine the clinical dose to achieve the optimal rifampin exposure in patients.
- The SCC rate in patients treated with combination regimen containing rifampin at 10 mg/kg of body weight/day was 73%, the mean time to SCC was 108 days, and the mean duration of therapy was 382 days.
- The target attainment probability of the standard 10-mg/kg/day dose fell below 90% even at the MIC of 0.0625 mg/L.
- Despite the initial kill, there was *M. kansasii* regrowth with the standard rifampin dose in the HFS-Mkn model. Doses higher than 10 mg/kg/day, in combination with other drugs, need to be evaluated for better treatment outcome.



RIF PK and *M. kansasii* – hollow fiber model

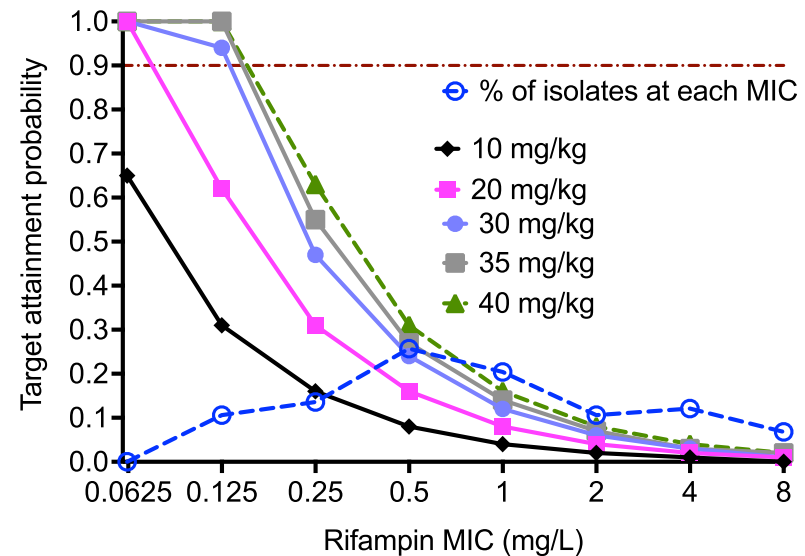
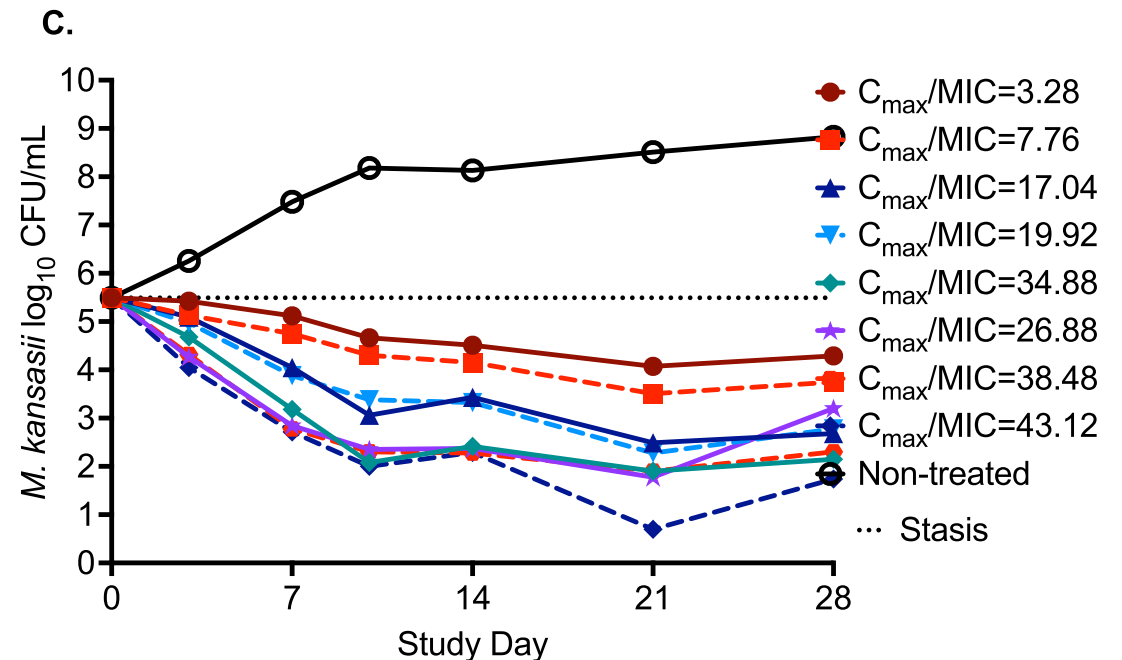


FIG 4 *In silico* simulations of different rifampin doses for PK/PD target attainment. The target attainment probability of different rifampin doses for the probability to achieve an $fC_{\max}/MIC$ ratio of 34.22 was calculated. All simulated doses failed to achieve the target attainment in 90% of the patients beyond a MIC of 0.125 mg/L.



Therapeutic drug monitoring in NTM therapy

Text box 2 Recommendations for TDM in NTM disease

Efficacy	Information on PK/PD targets on drugs used for NTM is scarce. TDM for efficacy is preferably guided by PK/PD targets but if these are lacking it would help to target normal exposure in patients with low exposure not responding to therapy
Toxicity	In the case of presumed drug-related toxicity, dose adjustment is suggested when high drug concentrations are observed at a standard dose
Drug–drug interactions	Drug–drug interactions can be managed as usual and TDM can be used to verify if exposure is within the normal range for that particular drug
Renal or hepatic function problems	For renally excreted or hepatically metabolized drugs, dosages can be adjusted as recommended by guidelines and TDM can be used to verify if exposure is within the normal range for that particular drug
Comorbidities (e.g., diabetes mellitus, HIV, CF)	As treatment in patients with comorbidities is often accompanied with complications, it is recommended to evaluate drug exposure in situations where these may arise
Sampling	At least 2 samples should be collected during the dose interval to assess drug exposure. A single sample often does not provide sufficient information as delayed absorption or reduced clearance is imperceptible

CF cystic fibrosis, *HIV* human immunodeficiency virus, *NTM* nontuberculous mycobacteria, *PD* pharmacodynamic, *PK* pharmacokinetic, *TDM* therapeutic drug monitoring

Therapeutic drug monitoring in NTM therapy

Drug	NTM	PK/PD	PK/PD target	AUC	Cmax (mg/L)	TDM for efficacy	TDM for toxicity
RIF	-	AUC/MIC	-	38.73 ± 4.33	5.79 ± 2.14	Yes	Yes
INH	-	AUC/MIC	-	-	3-5	Yes	Yes
EMB	MAC	AUC/MIC Cmax/MIC	-	1.23	2-6	Yes	Yes
STR	MAC	-	-	-	44 (33-58)	Yes	Yes
AMK	MAC	Cmax/MIC	>8/12	153 ± 51	55.3 ± 16.9	Yes	Yes
	Mabs	Cmax/MIC	>3.2	-	79 (54-98)	Yes	Yes
KAN	MAC	-	-	-	44 (32-65)	Yes	Yes
TGC	Mabs	AUC/MIC	36-44	-	No data	Yes	Yes
TZD	MAC	AUC/MIC	24-37	-	No data	Yes	?
CZA/AVI	MAC	ft>MIC	>52%	-	No data	Yes	?



Clinical Pharmacokinetic and Pharmacodynamic Considerations in the Drug Treatment of Non-Tuberculous Mycobacteria in Cystic Fibrosis

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Accepted: 28 February 2021 / Published online: 13 May 2021
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Abstract

Non-tuberculous mycobacteria (NTM) are an emerging group of pulmonary infectious pathogens of increasing importance to the management of patients with cystic fibrosis (CF). NTM include slow-growing mycobacteria such as *Mycobacterium avium* complex (MAC) and rapidly growing mycobacteria such as *Mycobacterium abscessus*. The incidence of NTM in the CF population is increasing and infection contributes to significant morbidity to the patient and costs to the health system. Treating *M. abscessus* requires the combination of multiple costly antibiotics for months, with potentially significant toxicity associated with treatment. Although international guidelines for the treatment of NTM infection in CF are available, there are a lack of robust pharmacokinetic studies in CF patients to inform dosing and drug choice. This paper aims to outline the pharmacokinetic and pharmacodynamic factors informing the optimal treatment of NTM infections in CF.

Key Points

The treatment of non-tuberculous mycobacteria (NTM) in cystic fibrosis (CF) is complicated by differing pharmacokinetics to the non-CF population.

NTM treatment requires the prolonged use of repurposed antibiotics and is characterized by relatively low success rates and high toxicity.

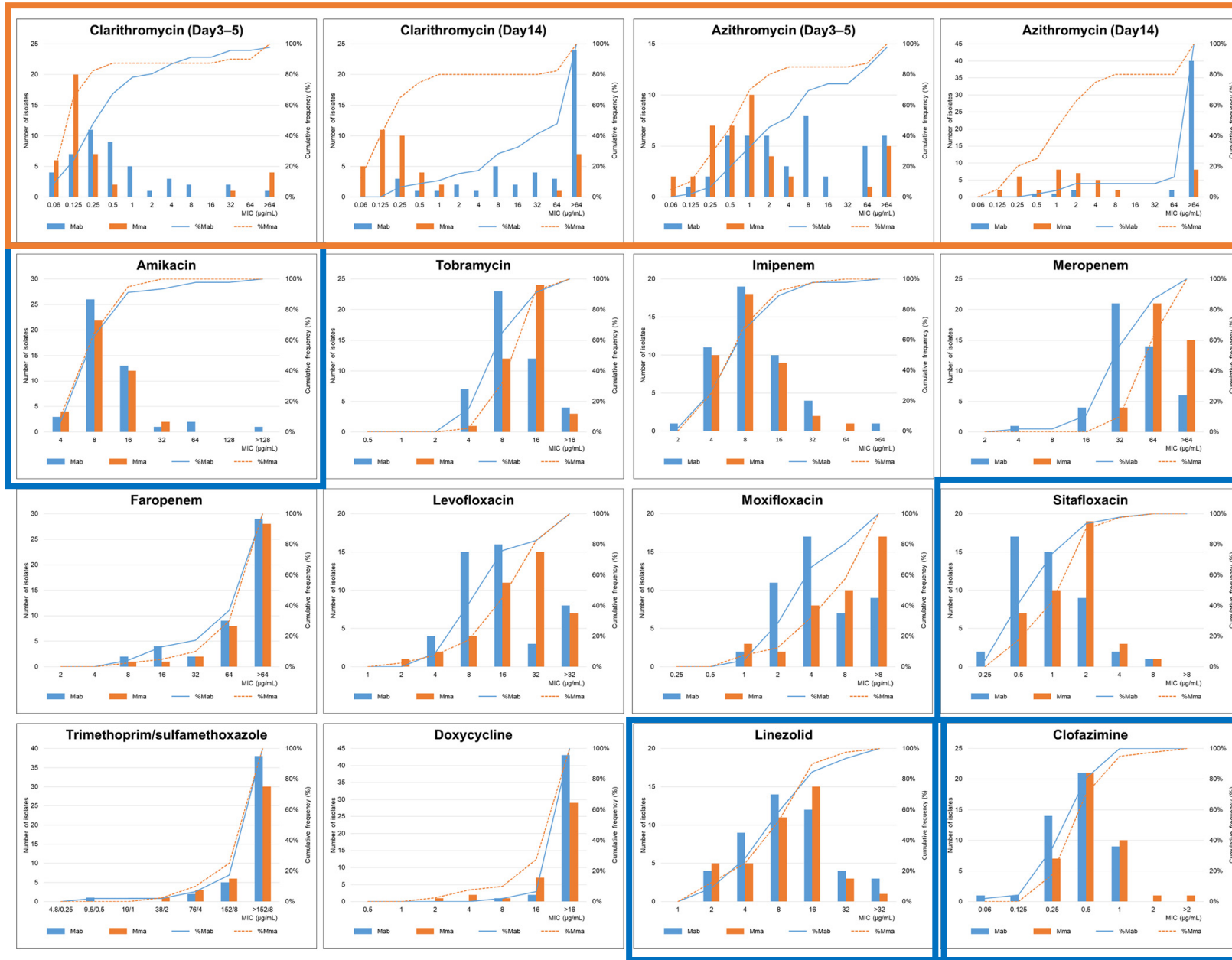
The increasing use of CF transmembrane regulator (CFTR) modulator drugs poses challenges, with potential drug–drug interactions that may limit therapeutic options.

Long-term macrolide in bronchiectatic patients (and the risk of NTM)

- US bronchiectatic registry, non previous NTM
- 410 subjects (out of 3472): 91 macrolide and 319 non-macrolide
 - Similar patients' characteristics
- At least one positive culture in 3/91 (3.3%) vs. 44/319 (13.8%)
 - OR=0.21; 95% CI, 0.06-0.70; P=.005
 - No macro-R observed (in 2/3 available) in the macro group

MIC for Mabs

Fujiwara K, Microb Spectrum 2021



MIC for Mabs

Fujiwara K, Microb Spectrum 2021

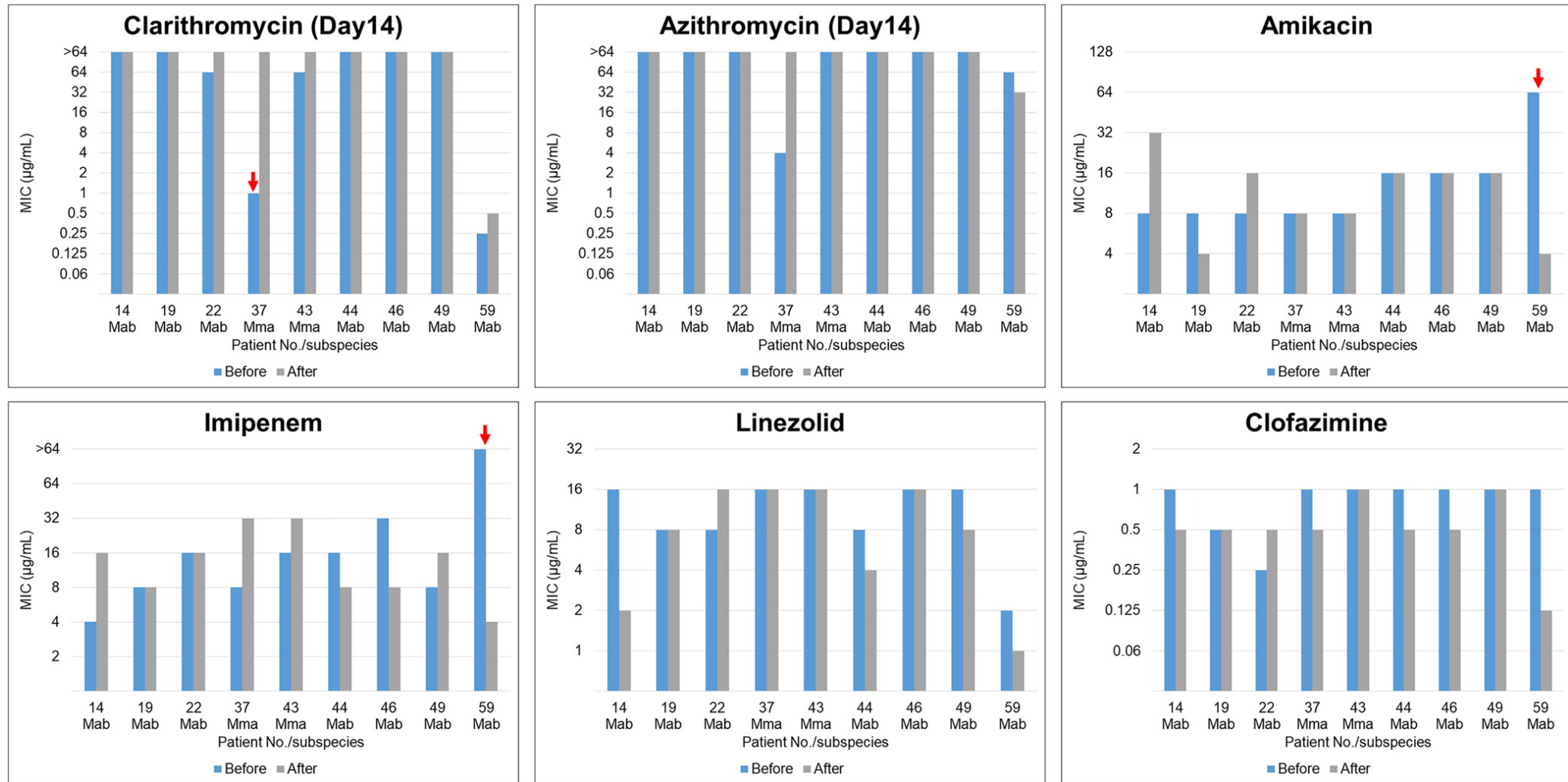


FIG 2 Changes in MICs of antibiotics among isolates were obtained from nine identical patients. Obvious MIC changes were observed in isolates from two cases (indicated by arrows): from susceptible to resistance to clarithromycin and from resistant to susceptible to amikacin and imipenem. Mab, *Mycobacterium abscessus* subsp. *abscessus*; Mma, *Mycobacterium abscessus* subsp. *massiliense*.

Prognosis

St. George Respiratory Questionnaire (SGRQ)

St. George's Respiratory Questionnaire (SGRQ)

Name of questionnaire	St. George's Respiratory Questionnaire (SGRQ)
Type of questionnaire-description	Disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.
Number of items	50 items
Number of domains & categories	2 parts (3 components)
Name of categories/domains	Part 1 : Symptoms component (frequency & severity) with a 1, 3 or 12-month recall (best performance with 3- and 12-month recall); Part 2: Activities that cause or are limited by breathlessness; Impact components (social functioning, psychological disturbances resulting from airways disease) refer to current state as the recall.
Scaling of items	Part I (Symptoms): several scales; Part II (Activity and Impacts): dichotomous (true/false) except last question (4-point Likert scale)
Scoring	Scores range from 0 to 100, with higher scores indicating more limitations.
Test-retest reproducibility	Yes. For the American version, the intraclass correlations were 0.795 to 0.900
Internal consistency	Reported (Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. Am Rev Respir Dis 1992;145:1321-1327). For the American version, Cronbach's α was > 0.70 for all components (Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. Clin Ther. 2000 Sep, 22(9):1121-45).
Validity	Reported: - Significant correlations between total score and presence of cough, sputum, and wheeze; - Significant correlations between symptom, activity, and impact domains and other measures of disease activity (FEV1, FVC, SaO2 at rest, 6-MWD, MRC dyspnea grade, anxiety score, depression score, Sickness Impact Profile (SIP) total score, SIP physical and psychosocial domains) (Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. Am Rev Respir Dis 1992, 145: 1321-1327; Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. Resp Med 1991, 85(suppl):25-31).
Minimally important difference	Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment (Jones PW and the Nedocromil Sodium Quality of Life Study Group. Quality of life, symptoms, and pulmonary function in asthma: long-term treatment with nedocromil sodium examined in a controlled multicentre trial. Eur Respir J 1994, 7:55-62; Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J. 2002 Mar, 19(3):398-404).

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

ID NUMBER:

FORM CODE: SGR

VERSION: 3.0 10/24/2017

Event:

0a) Date of Collection

/

/

0b) Staff Code

Instructions:

This form should be completed during the participant's clinic visit. Please read the script exactly as written.

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please ask if you have difficulty understanding the questions. Do not spend too long deciding about your answers.

0c) Please pick one response to show how you describe your current health:

Very good₁

Good₂

Fair₃

Poor₄

Very Poor₅

The following questions ask about your chest trouble. Please answer as it applies to you.

PART 1

1) I cough:

Most days a week₁

Several days a week₂

Only with respiratory infections₄

Not at all₅

2) I bring up phlegm (sputum):

Most days a week₁

Several days a week₂

Only with respiratory infections₄

Not at all₅

3) I have shortness of breath:

Most days a week₁

Several days a week₂

Not at all₅

4) I have attacks of wheezing:

Most days a week₁

Several days a week₂

A few days a month₃

Only with respiratory infections₄

Not at all₅

5) How many attacks of chest trouble did you have during the last year?

3 or more attacks₁

1 or 2 attacks₂

None₃

6) How often do you have good days (with few respiratory problems)?

No good days₁

A few good days₂

Most days are good₃

Every day is good₄

7) If you have a wheeze, is it worse when you get up in the morning?

No₀

Yes₁

PART 2

8) How would you describe your respiratory problems?

Cause me a lot of problems or are the most important physical problem I have₁

Cause me a few problems₂

Cause no problems₃

9) Questions about what activities usually make you feel breathless. For each statement, please tell me which applies to you these days.

	False ₀	True ₁
9a) Washing or dressing yourself	☐	☐
9b) Walking around the house	☐	☐
9c) Walking outside on the level ground	☐	☐
9d) Walking up a flight of stairs	☐	☐
9e) Walking up hills	☐	☐

10) Some more questions about your cough and breathlessness. For each statement, please tell me which applies to you these days.

	False ₀	True ₁
10a) Coughing hurts	☐	☐
10b) Coughing makes me tired	☐	☐
10c) I am short of breath when I talk	☐	☐
10d) I am short of breath when I bend over	☐	☐
10e) My cough or breathing disturbs my sleep	☐	☐
10f) I get exhausted easily	☐	☐

11) Questions about other effects that your chest trouble may have on you. For each statement, please tell me which applies to you these days.

	False ₀	True ₁
11a) My cough or breathing is embarrassing in public	☐	☐
11b) My respiratory problems are a nuisance to my family, friends, or neighbors	☐	☐
11c) I get afraid or panic when I cannot catch my breath	☐	☐
11d) I feel that I am not in control of my respiratory problems	☐	☐
11e) I have become frail or an invalid because of my respiratory problems	☐	☐
11f) Exercise is not safe for me	☐	☐
11g) Everything seems too much of an effort	☐	☐

12) These are questions about how your activities might be affected by your respiratory problems. For each statement, please tell me which applies to you because of your breathing.

	False ₀	True ₁
12a) I take a long time to get washed or dressed	☐	☐
12b) I cannot take a bath or shower, or I take a long time to do it	☐	☐
12c) I walk slower than other people, or I stop to rest	☐	☐
12d) Jobs such as house chores take a long time, or I have to stop to rest	☐	☐
12e) If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
12f) If I hurry or walk fast, I have to stop or slow down	☐	☐
12g) My breathing makes it difficult to do things such as walk up hills, carry things up stairs, do light gardening such as weeding, dance, bowl, or play golf	☐	☐
12h) My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis, or swim	☐	☐

13) We would like to know how your chest usually affects your daily life. For each statement, please tell me which applies to you because of your breathing.

	False ₀	True ₁
13a) I cannot play sports or do other physical activities	☐	☐
13b) I cannot go out for entertainment or recreation	☐	☐
13c) I cannot go out of the house to do the shopping	☐	☐
13d) I cannot do household chores	☐	☐
13e) I cannot move far from my bed or chair	☐	☐

14) How do your respiratory problems affect you? Please pick one response.

They do not stop me from doing anything I would like to do₁

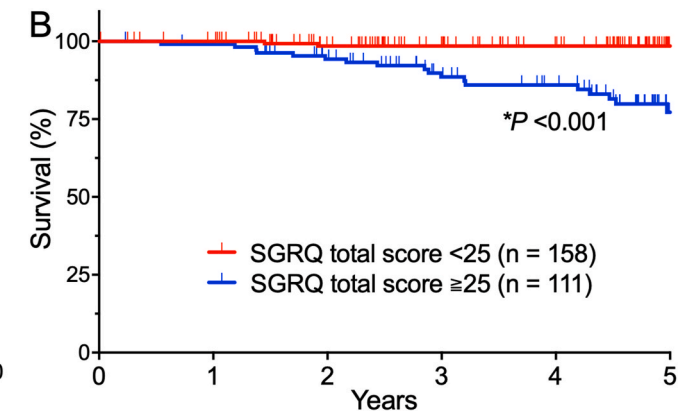
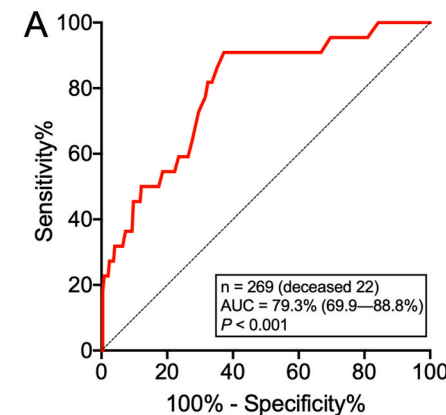
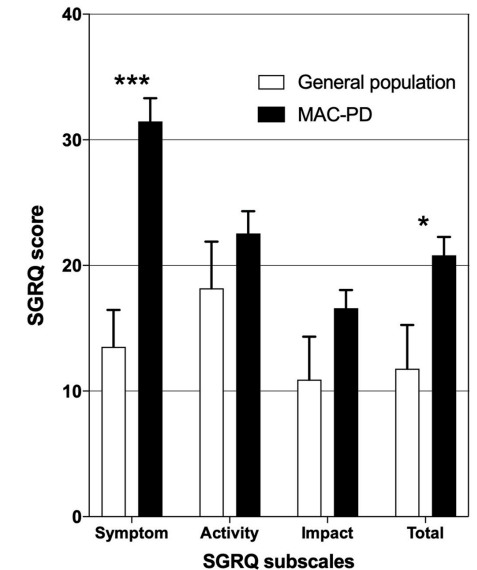
They stop me from doing one or two things I would like to do₂

They stop me from doing most of the things I would like to do₃

They stop me from doing everything I would like to do₄

SGRQ in NTM-LD patients

- Prospective observational study (2012-2018)
- 269 pts with MAC-PD
- **Age- and sex-matched SGRQ scores indicated significantly greater impairment in patients with MAC-PD than in the general population ($P < 0.001$)**
- Patients with a greater decline from baseline FEV1 (% predicted) exhibited significantly worse impairment in the SGRQ total score (mean $\pm$ SE, 4.69 ± 10.9 points, $P = 0.001$).
- On multivariable Cox proportional hazards regression analysis, **the SGRQ total score ≥ 25 was an independent risk factor for mortality (adjusted hazard ratio, 5.90; 95% confidence interval, 1.65–37.7)** as well as age, body mass index, and forced vital capacity (FVC).
- Mixed-effect model results showed a significant association between SGRQ symptom/total scores and forced expiratory volume in 1 s (FEV1), FVC, and diffusing carbon monoxide capacity. Older age, a positive smear, non-nodular/bronchiectatic form, and cavity regions were associated with SGRQ total score deterioration.



RESEARCH

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The 6-minute walk test predicts mortality in a pulmonary nontuberculous mycobacteria-predominant bronchiectasis cohort

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Abstract

Background: Bronchiectasis is a chronic lung condition frequently associated with nontuberculous mycobacteria pulmonary (NTM) disease. Persons with these conditions are at increased risk of mortality. Patient reported outcome (PRO) instruments and the 6-minute walk test (6MWT) have been shown to predict mortality for several lung conditions, but these measures have not been fully evaluated for bronchiectasis and NTM.

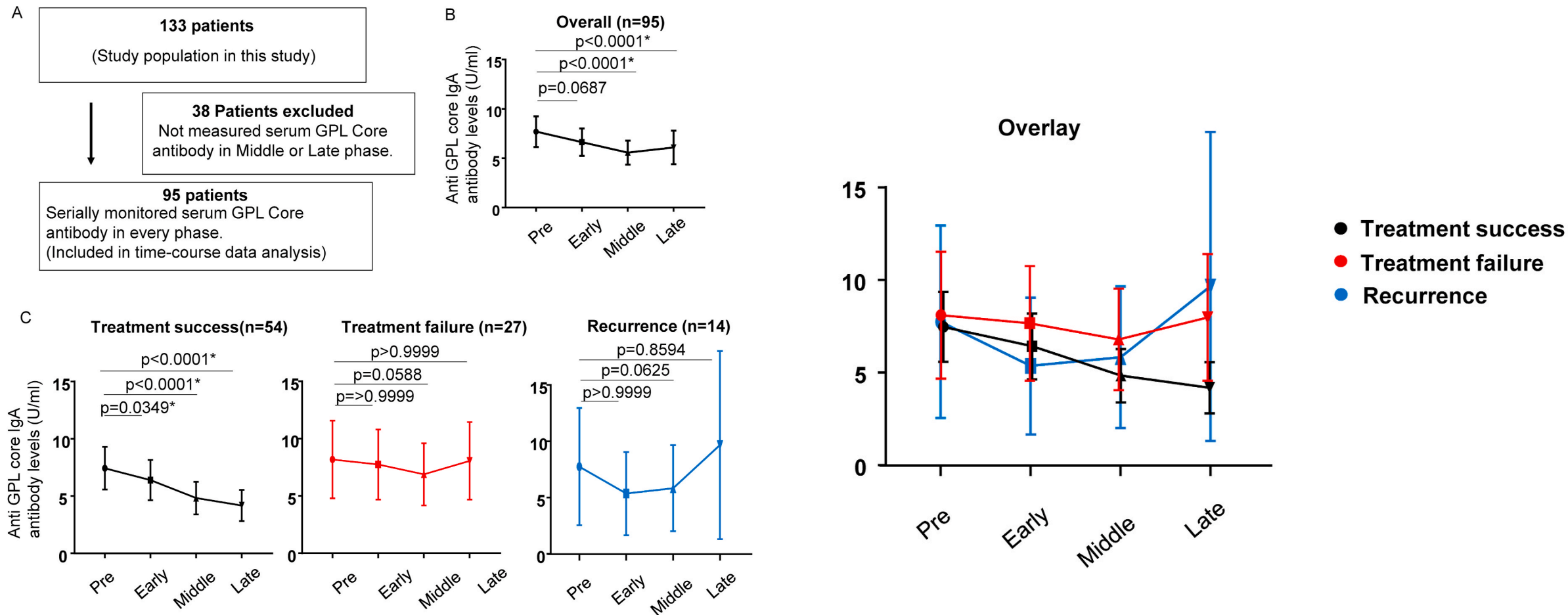
Methods: We conducted a retrospective cohort study among adult patients enrolled in a natural history study of bronchiectasis at the National Heart, Lung, and Blood Institute. Electronic medical records were queried for demographic, clinical, microbiologic, radiographic, and PRO instrument data: St. George's Respiratory Questionnaire (SGRQ), Medical Research Council Dyspnea Scale, and the Pulmonary Symptom Severity Score (PSSS). The study baseline date was defined as the patient's first visit after January 1st, 2015 with a SGRQ or 6MWT completed. Follow-up was defined as the interval between the study baseline visit and date of death or December 31st, 2019. Sex-stratified Cox proportional-hazards regression was conducted to identify predictors of mortality. Separate models were run for each PRO and 6MWT measure, controlling for age, body mass index (BMI), fibrocavitary disease status, and *M. abscessus* infection.

Results: In multivariable Cox proportional-hazards regression models, the PSSS-severity (aHR 1.29, 95% CI 1.04–1.59), the 6MWT total distance walked (aHR 0.938, 95% CI 0.896–0.981) and distance saturation product (aHR 0.930, 95% CI 0.887–0.974) independently predicted mortality. In addition, BMI was significantly predictive of mortality in all models.

Conclusions: The 6MWT and a PRO instrument capturing symptom severity are independently predictive of mortality in our cohort of bronchiectasis patients.

Keywords: Bronchiectasis, Nontuberculous mycobacteria, Mortality, Patient reported outcomes, Health-related quality of life, 6-Minute walk test

Serum IgA against Glycopeptidolipid Core in MAC-LD (2)



Impact of Time Between Diagnosis and Treatment on Culture Conversion and All-Cause Mortality

- 712 patients who received antibiotics for 6 or more months after diagnosis of NTM-PD (1997 – 2013).
- Thirty-eight percent of study patients had mild disease, 48% had moderate disease, and 14% had severe disease.
- **The median waiting period without antibiotics among all patients was 4.8 (interquartile range, 1.3-20.8) months.**
- **After treatment initiation, 479 (67%) patients achieved culture conversion within 6 months, and 135 (19%) patients died.**
- In univariable and multivariable models adjusted for BACES (BMI, Age, Cavities, ESR, sex) severity, **no association between the waiting period and 6-month culture conversion or death was identified.**

TABLE 3] Effect of 6-Months or 12-Months Culture Conversion on Death in Patients With NTM-PD

Patient Group	Treatment for ≥ 6 mo (n = 712) ^a	Treatment ≥ 12 mo (n = 676) ^a
Death	n = 135	n = 116
HR of conversion within 6 or 12 mo for death		
Crude HR (95% CI, P)	0.46 (0.33–0.65, < .001) ^b	0.42 (0.29–0.61, < .001) ^c
Model 1, adjusted HR (95% CI, P)	0.51 (0.35–0.74, < .001) ^b	0.51 (0.33–0.78, .002) ^c
Model 2, adjusted HR (95% CI, P)	0.52 (0.35–0.76, < .001) ^b	0.52 (0.34–0.80, .003) ^c
Model 3, adjusted HR (95% CI, P)	0.52 (0.36–0.77, < .001) ^b	0.52 (0.34–0.81, .003) ^c

Early sputum conversion and outcome in Mabs

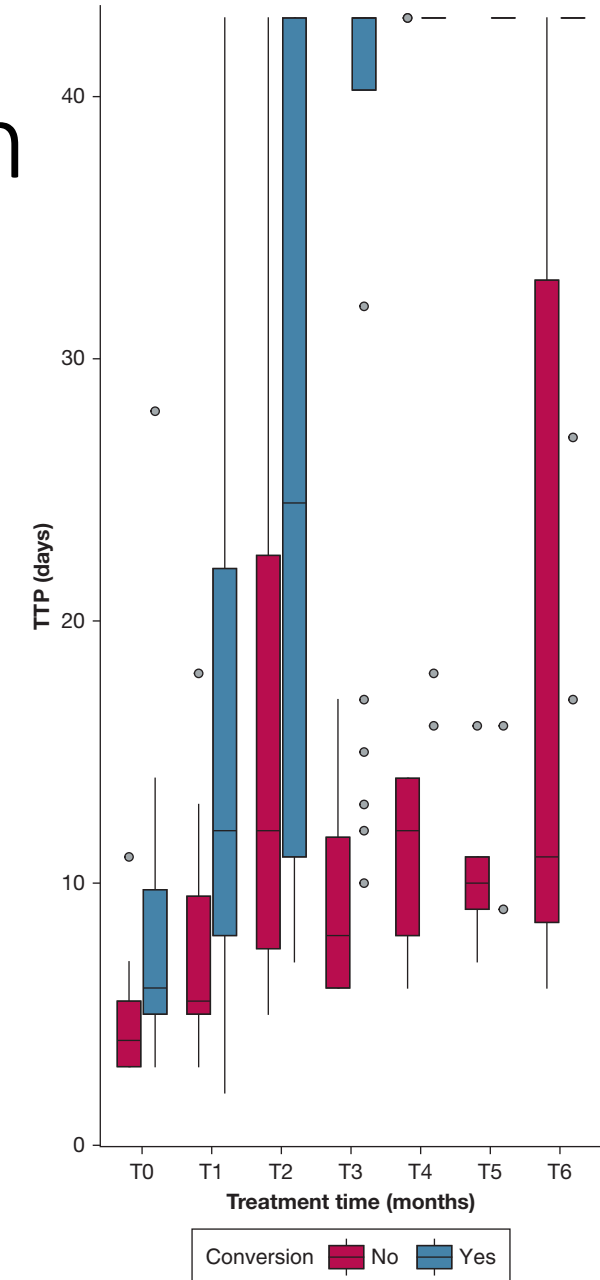
- *M. abscessus* PD treated with i.v. amikacin for ≥ 8 weeks and i.v. β -lactams for ≥ 2 weeks (2005–2019).
- Sputum sample with at least a 1-month interval after treatment initiation
- Culture conversion and microbiological cure at 1 year was determined
- 57 patients
 - Mean age was 58.6 years and 68.4% were female
 - Mean BMI was 20.3 kg/m².
 - Positive sputum in 71.9% of patients
 - 45.6% of patients showed cavitary lesions.
 - Inducible resistance to clarithromycin in 73.7% (42/57)
 - Median duration of i.v. amikacin and β -lactam: 26.9 weeks and 8.3 weeks
- **Overall, the microbiological cure rate was 31.6% (18/57)**

TTP and sputum conversion

Mycobacterium Growth
Indicator Tube Time-To-
Positivity Can Serve As an
Early Biomarker of
Treatment Response in
Mycobacterium avium
Complex Pulmonary Disease

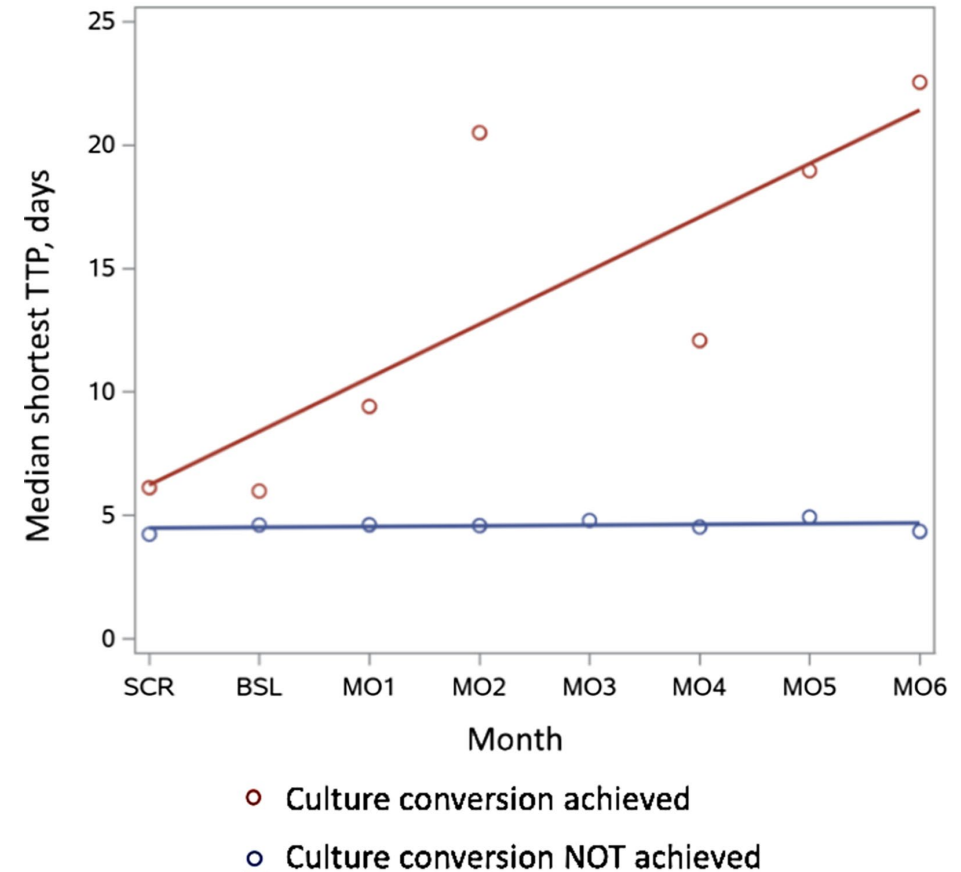


Culture conversion	Yes (n = 34)	No (n = 15)	Total (N = 49)
Female patients, No. (%)	19 (56)	8 (53)	27 (55)
Age, mean $\pm$ SD, y	65.59 $\pm$ 9.32	60.53 $\pm$ 10.45	64.0 $\pm$ 9.9
Fibrocavitary disease, No. (%)	18 (53)	10 (67)	28
Nodular-bronchiectatic disease, No. (%)	16 (47)	5 (33)	21
<i>M avium</i> , No.	16	6	22
<i>M intracellulare</i> , No.	8	4	12
<i>M chimaera</i> , No.	10	5	15
Baseline time to positivity, mean $\pm$ SD, d	7.68 $\pm$ 4.64	4.87 $\pm$ 2.20	6.82 $\pm$ 4.23
Time to positivity after 3 mo, mean $\pm$ SD, d	36.38 $\pm$ 12.30	9.75 $\pm$ 5.19	32.57 $\pm$ 14.89
Samples per patient, mean $\pm$ SD, No.	5.32 $\pm$ 1.20	4.87 $\pm$ 1.46	5.18 $\pm$ 1.29
3-Drug regimen, No. (%)	27 (79)	13 (87)	40 ^a
4/5-Drug regimen, No. (%)	7 (21)	2 (13)	9 ^b
Cure at end of treatment, No. (%)	22 (65)	2 (13)	24 (49)



TTP and sputum conversion (2)

- 71 participants
- **Median TTP at screening was longer in those participants who subsequently achieved** vs. did not achieve **culture conversion (10.5 [IQR 9.4] days vs. 4.2 [IQR 2.8] days, $p = 0.0002$).**
- Individuals with culture conversion by study treatment month 6 were more likely to have a screening TTP > 5 days compared to those who did not achieve culture conversion (OR 15.4, 95% CI 1.9, 716.7, $p = 0.0037$) and had increasing TTPs over time.

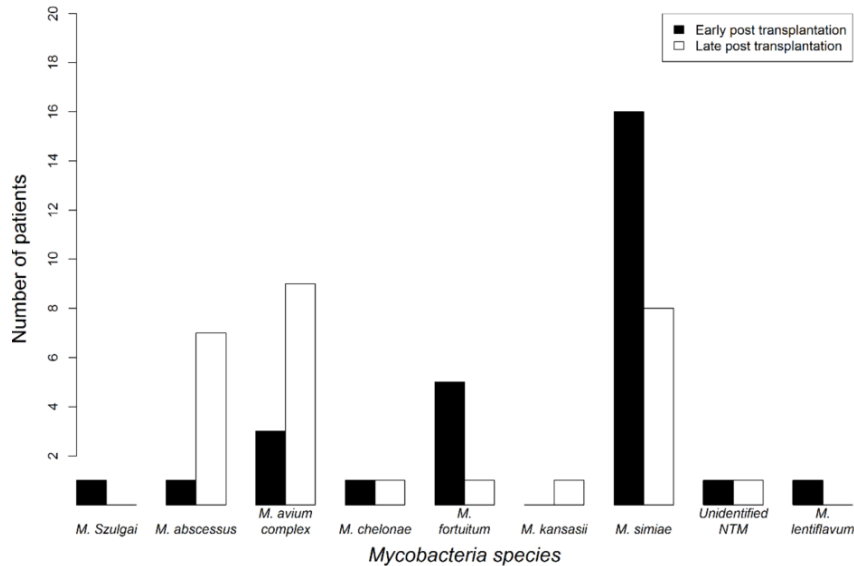


Early sputum conversion in Mabs (2)

Months since treatment initiation	Sensitivity	Specificity	PPV	NPV	κ
<i>M. abscessus</i> isolates with IR ($n = 42$)					
1	0.18	0.94	0.50	0.76	0.15
2	0.45	0.84	0.50	0.81	0.30
3	0.64	0.84	0.58	0.87	0.46
4	0.73	0.87	0.67	0.90	0.58
5	0.73	0.87	0.67	0.90	0.58
6	0.73	0.90	0.73	0.90	0.63
7	0.91	0.90	0.77	0.97	0.77
8	0.91	0.90	0.77	0.97	0.77
9	0.91	0.94	0.83	0.97	0.82
10	0.91	0.94	0.83	0.97	0.82
11	0.82	0.97	0.90	0.94	0.81
<i>M. abscessus</i> isolates without IR ($n = 15$)					
1	0.57	1.00	1.00	0.73	0.59
2	0.71	1.00	1.00	0.80	0.73
3	0.86	1.00	1.00	0.89	0.87
4	1.00	0.88	0.88	1.00	0.87
5	1.00	0.88	0.88	1.00	0.87
6	1.00	1.00	1.00	1.00	1.00
7	1.00	1.00	1.00	1.00	1.00
8	1.00	1.00	1.00	1.00	1.00
9	1.00	1.00	1.00	1.00	1.00
10	1.00	1.00	1.00	1.00	1.00
11	1.00	1.00	1.00	1.00	1.00

NTM in Lung Transplant Recipients

Figure 2. Spectrum of Nontuberculous Mycobacteria Species in the Early and Late Posttransplant Periods According to 6-Month Median Cut-off

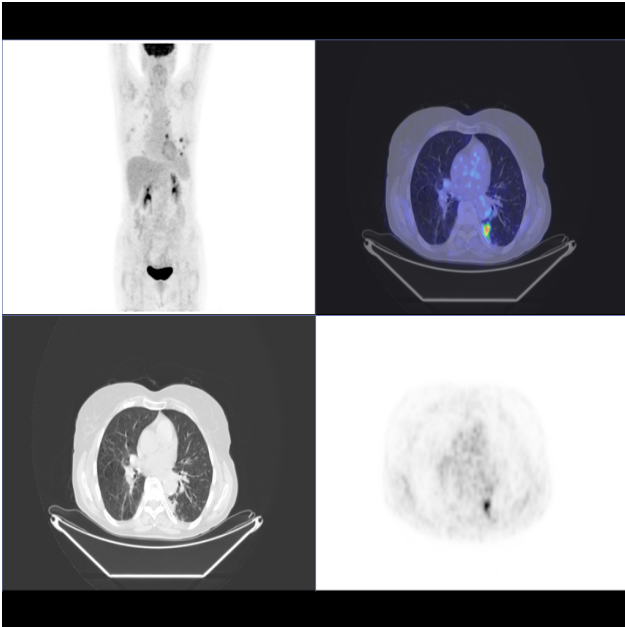


- Israel, monocentric, LT recipients, 1997-2019
- 58/690 (8.4%)
 - Mycobacterium simiae (n = 24), avium complex (n = 12), abscessus (n = 9), fortuitum (n = 6) and others
- **Early (<6 months) more common *M simiae* and *M fortuitum* vs. M abscessus and MAC in the late period**
- No difference in FEV1 (NTM+ vs. NTM-)
- **NTM acquisition was significantly associated with decreased survival (relative risk of 2.41, 95% CI, 1.70-3.43; P < .001).**

FDG-PET in pazienti con NTM

Autori	N pazienti	SUV medio	N medio lesioni	Specie
Kawate E.	2	9	1	M. avium
Matsuyama W	1	5.1	1	M. intracellulare
Nagai A	1	10.8	1	M.avium
Kwon YS	1	11.5	1	M. abscessus
Nakagawa N	1	4.8	1	M.avium
Tanaka S	1	-	1	Mycolicibacterium phlei
Namkoong H	1	Riferito solo ai linfonodi	-	MAC
Del Giudice	6	3.6	2	M. kansasii, M. xenopi, MAC
Zhuang H	1	8.1	-	M. intracellulare
Kato A	1	26.9	-	M.avium
Bandoh S	2	2.86	-	MAC, M. intracellulare
Demura Y	6	6.2	1	MAC
Talwar A	1	4.2	1	M.chelonae
Abe M	1	HIGH	1	M. kansasii
Nishino K	6	8.9	1	M. intracellulare, M.avium
Gaviraghi A	20	4.20	2	14 MAC

FDG-PET in NTM-LD: SCENARI CLINICI



1. INIZIARE O NON INIZIARE TERAPIA (DD!)
2. INTERROMPERE TERAPIA SENZA CRITERIO MICROBIOLOGICO
3. ATTEGGIAMENTI IN CASO DI RECIDIVA

Pipeline

Discovery		Phase I/II	Phase III	Phase IV
LCB01-0371 - Target 50S ribosome - For <i>M. abs</i>	Clofazimine* - Target NDH-2 - For <i>M. abs</i>	Clofazimine - Target NDH-2 - For <i>M. avium</i> PD	Liposomal amikacin for inhalation (LAI) - Target 30S ribosome - For refractory MAC PD	Linezolid - Target 50S ribosome - For NTM disease
PIPD1 - Target MmpL3 - For <i>M. abs</i>	Tedizolid* - Target 50S ribosome - For NTM	Liposomal amikacin for inhalation (LAI) - Target 30S ribosome - For <i>M. abs</i> PD	Clarithromycin vs azithromycin - Target 50S ribosome - For MAC PD	
Indole-2-carboxamides - Target MmpL3 - For <i>M. abs</i>	Bedaquiline* - Target ATP synthase - For NTM	Nitric oxide - Enhance host defense - Produce reactive nitrogen intermediates - For CF patients with NTM (especially <i>M. abs</i>) - From AIT therapeutics	Clarithromycin vs moxifloxacin - Target DNA gyrase - For <i>M. xenopi</i> PD	
Thiacetazone derivatives - Target FAS-II dehydratase - For <i>M. avium</i> and <i>M. abs</i>	β-lactams with avibactam* - Target penicillin-binding protein - For <i>M. abs</i> and <i>M. avium</i>	Gaseous nitric oxide (gNO)^a - Enhance host defense - Produce reactive nitrogen intermediates - For NTM - Thiolanox[®] from novoteris		
	Rifabutin* - Target RNA polymerase - For <i>M. abs</i>			

Mechanism of action

- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid synthesis
- Other mechanisms

RESEARCH ARTICLE

Open Access

Hemoptysis requiring bronchial artery embolization in patients with nontuberculous mycobacterial lung disease



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Sung Shine Shim³ , Min Uk Kim⁴ , Sun Young Choi³  and Yon Ju Ryu^{2*} 

Abstract

Background: Although infections caused by nontuberculous mycobacteria (NTM) are increasing in prevalence, there are few data about hemoptysis in patients with NTM lung disease. This study investigated the characteristics and prognosis of hemoptysis secondary to NTM infection.

Methods: Following a retrospective review of cases managed between 2006 and 2016, 183 patients with NTM lung disease were enrolled and analyzed.

Results: Among 183 patients with NTM lung disease, *Mycobacterium intracellulare* ($n = 64$, 35%) was the major cause of NTM infection, followed by *M. avium* ($n = 59$, 32.2%) and *M. abscessus* complex ($n = 40$, 21.9%). Hemoptysis developed in 78 patients (42.6%), among whom 33 (42.3%) required bronchial artery embolization (BAE). Between patients with and without hemoptysis, there were no significant differences with respect to sex, radiographic manifestations, distribution over 3 lobes on chest computed tomography, history of pulmonary tuberculosis, antiplatelet or anticoagulation therapy, and species of NTM. However, mean age at diagnosis was significantly lower in the hemoptysis group in univariate and multivariate analyses (65.7 ± 12.8 vs. 59.7 ± 11.8 , $P = 0.002$, odds ratio: 0.969, 95% confidence interval: 0.944–0.996). Among patients with hemoptysis, those requiring medical therapy and those requiring BAE were not significantly different in terms of demographic characteristics, radiographic manifestations, and distribution over 3 lobes. All patients who received BAE showed immediate clinical improvement, no procedure-related complications, and none of them died during the period under review.

Conclusions: NTM lung disease patients commonly experienced hemoptysis without specific risk factors except for relatively young age. Although some patients with hemoptysis needed BAE, the success rate of BAE was high, and there were no serious complications associated with BAE.

Keywords: Mycobacterium infections, nontuberculous, Tuberculosis, Hemoptysis, Embolization, therapeutic

Role of Surgical Intervention (ATS/IDSA 2020)

In selected patients with NTM pulmonary disease, we suggest surgical resection as an adjuvant to medical therapy after expert consultation

- 15 observational studies (approximately 700 patients)
- Almost all of the patients who underwent surgery had received antimicrobial treatment before and after surgery.
- Cure rate of the NTM disease, death, and recurrences were not significantly different between medical and surgical therapy (3 studies)
- Although there was more culture conversion observed in the patients who underwent surgery, the quality of evidence was very low,
- Surgical complications (such as bronchopleural fistula, prolonged air leak, pneumonia) were observed in 7–35% of participants.

Multidisciplinary Management

- 
- Respiratory Medicine,
 - Infectious Diseases,
 - Microbiology,
 - Immunology,
 - Radiology,
 - Respiratory Physiotherapy,
 - Psicology/Psychiatry,
 - Food and Nutrition

Conclusioni

- La terapia delle micobatteriosi non tubercolari è al momento insoddisfacente con efficacia variabile ma nel range 50-75%
 - Efficacia microbiologica/clinica/radiologica
 - *M abscessus* più difficile da trattare
- Necessità di team multidisciplinare e di coinvolgimento del paziente
 - Sensibilità genotipica vs. fenotipica
 - Prognosi importante per decider inizio prima terapia e eventuali recidive/reinfezioni
- Abbiamo bisogno di RCTs (e di nuovi farmaci)