Cutting-edge treatment approaches for *M. avium* complex and *M. abscessus*-PD

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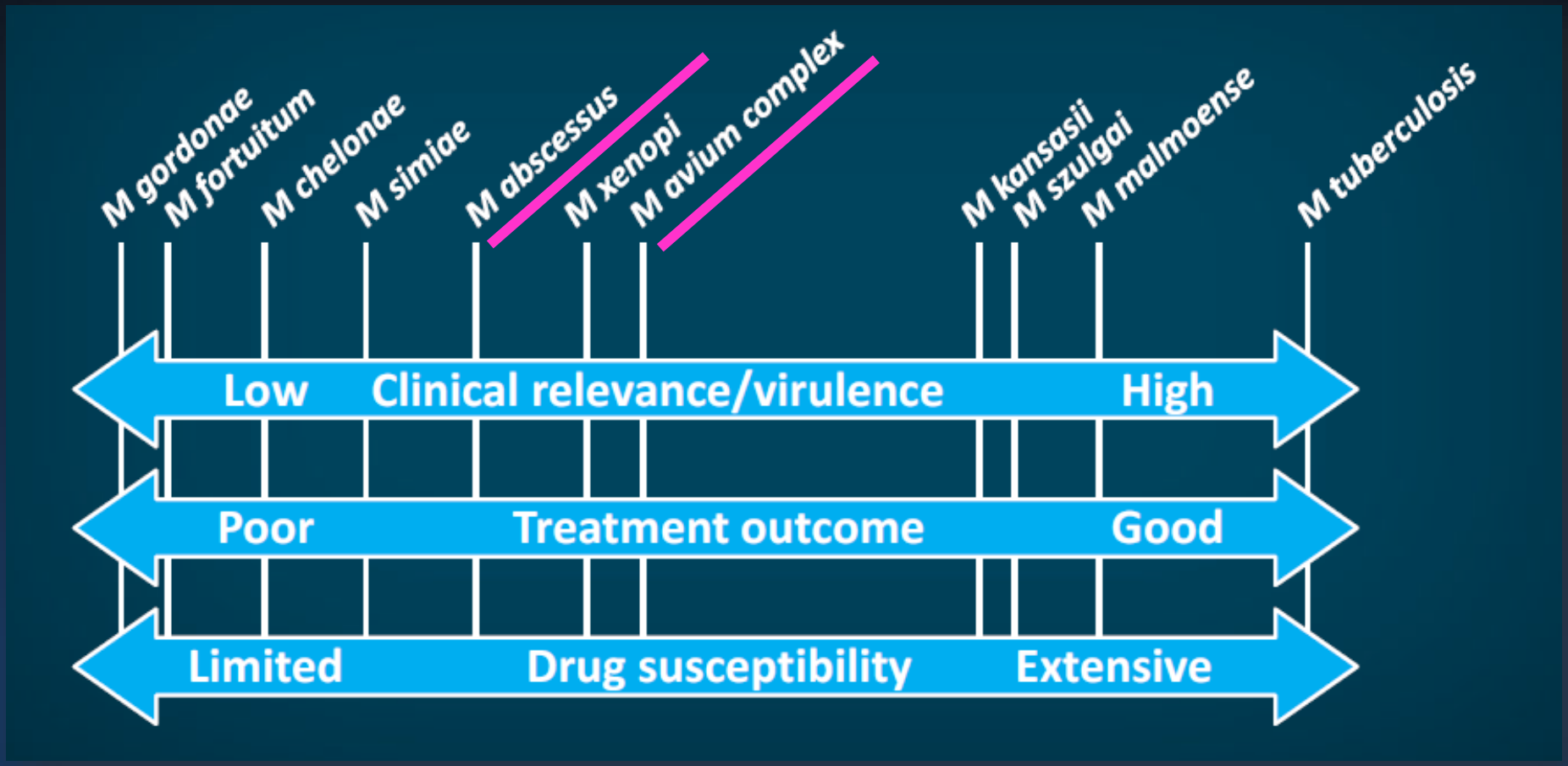
M. avium complex, M. abscessus

Most important pathogens



Infect Genet Evol 2012;12(4):832-7

Challenges in treating NTM-PD

- Antibiotic side effects and challenges with long-term injection use
- Absence of effective “oral" antibiotics
- Insufficient antibiotics with proven clinical correlation to MIC
- Difficulty in determining the right time to initiate treatment
- Repeated infections

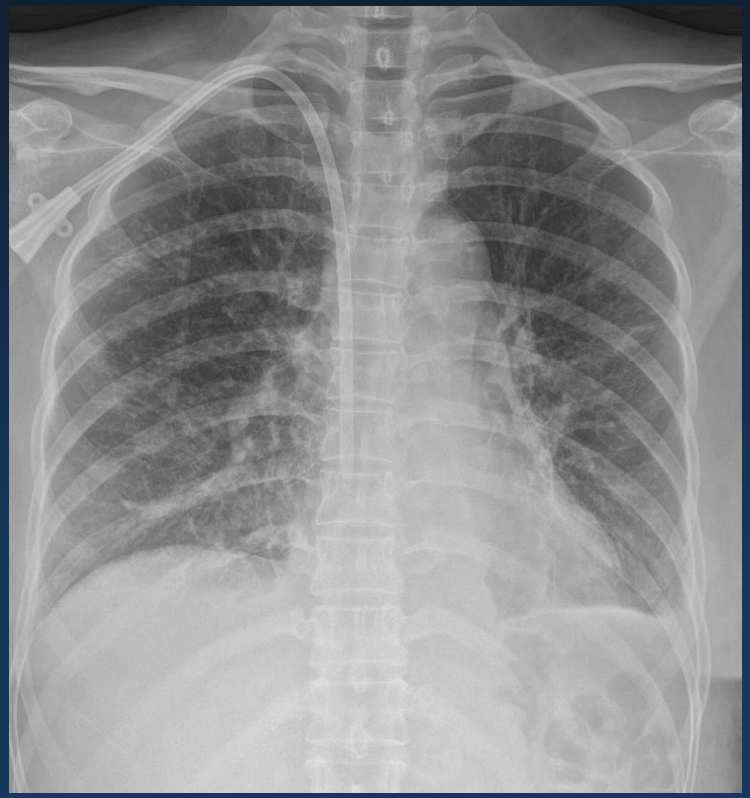
Gap between ideal and reality

CASE

Acute renal failure after rifampicin-nephritis

F/50, *M. intracellulare*, antibiotics - azithromycin ethambutol rifampicin

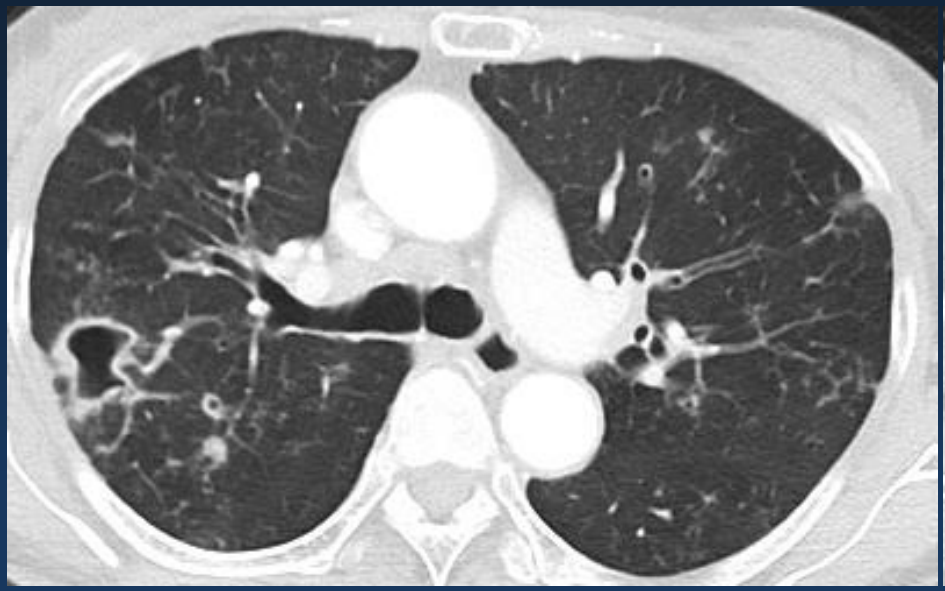
7 days later, Hemodialysis for 10 days due to anuria & pulmonary edema



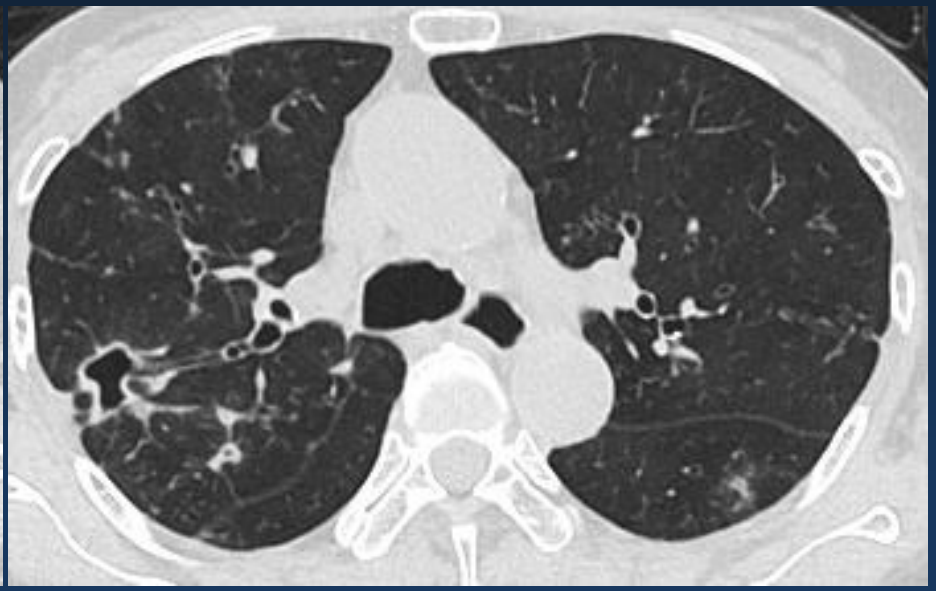
Treatment failure despite localized lesions

71/F, *M. abscessus*, Hemoptysis
Amikacin Prepenem Tigecycline Clofazimine Azithromycin
Antibiotics for more than 12 months

2021.06.28



2022.01.11



Persistent NTM culture positivity and intermittent hemoptysis

Venous stenosis caused by PICC

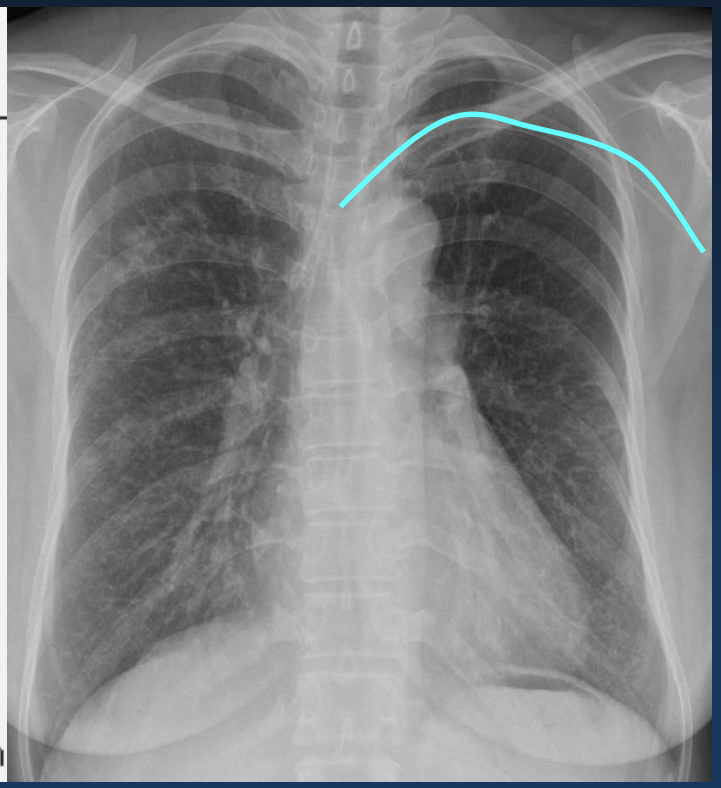
F/59, *M. abscessus*

Left basilic vein total occlusion after PICC

Left	Thrombus
Int. Jugular V.	Absence
Subclavian V.	Absence
Axillary V.	Absence
Brachial V.	Absence
Radial V.	Absence
Ulnar V.	Absence
Cephalic V.	Absence
Basilic V.	Total

▣ 결론 및 진단

1.Totally occluding thrombus in the left upper arm basilic vein



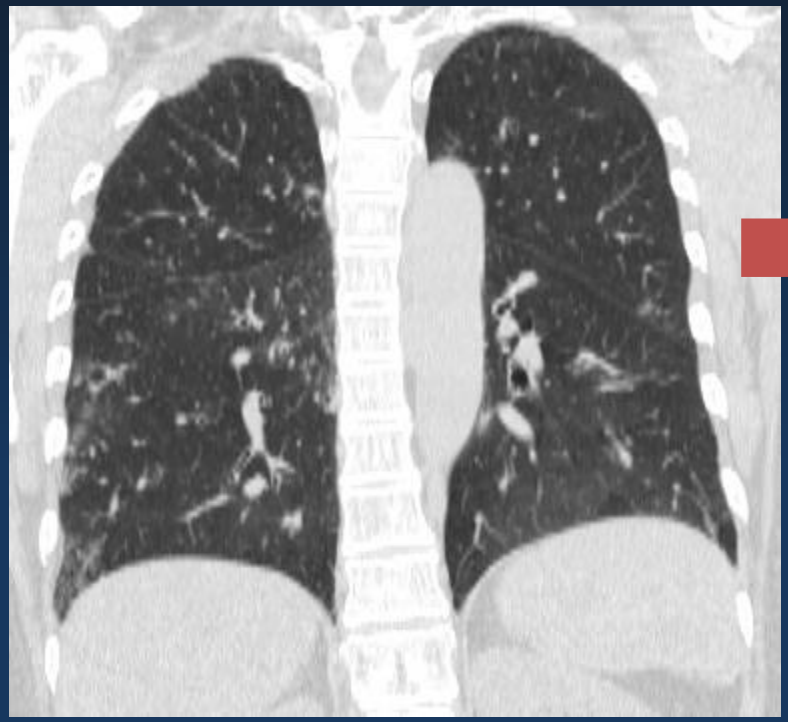
Result of patients and doctors delaying treatment

- severe destruction at the time of the decision to start antibiotics -

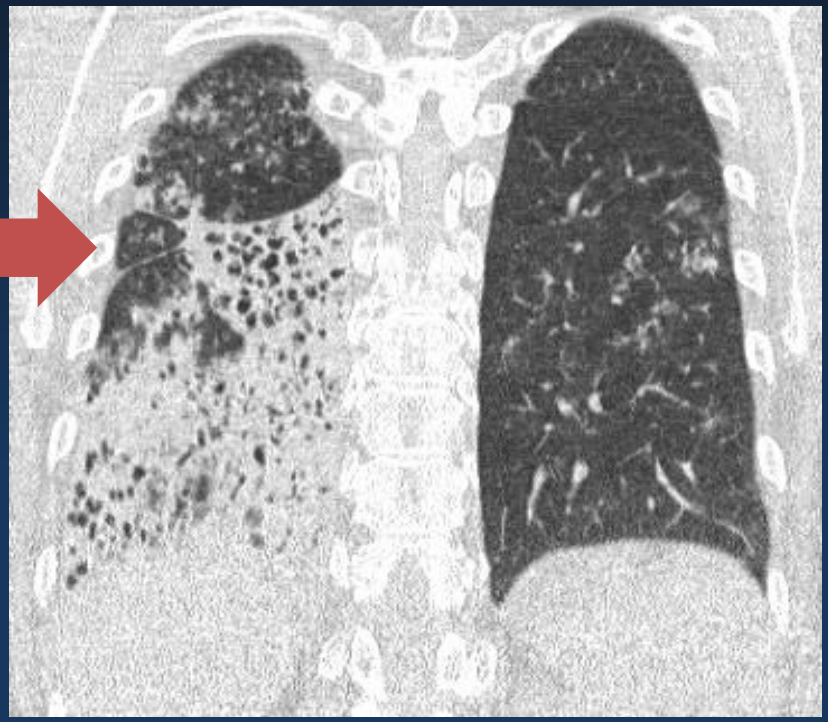
69/F, *M. abscessus*, Hemoptysis, Fever, Cough

Amikacin Prepenem Tigecycline Clofazimine Azithromycin Linezolid Rifabutin

2013.06.25 diagnosis

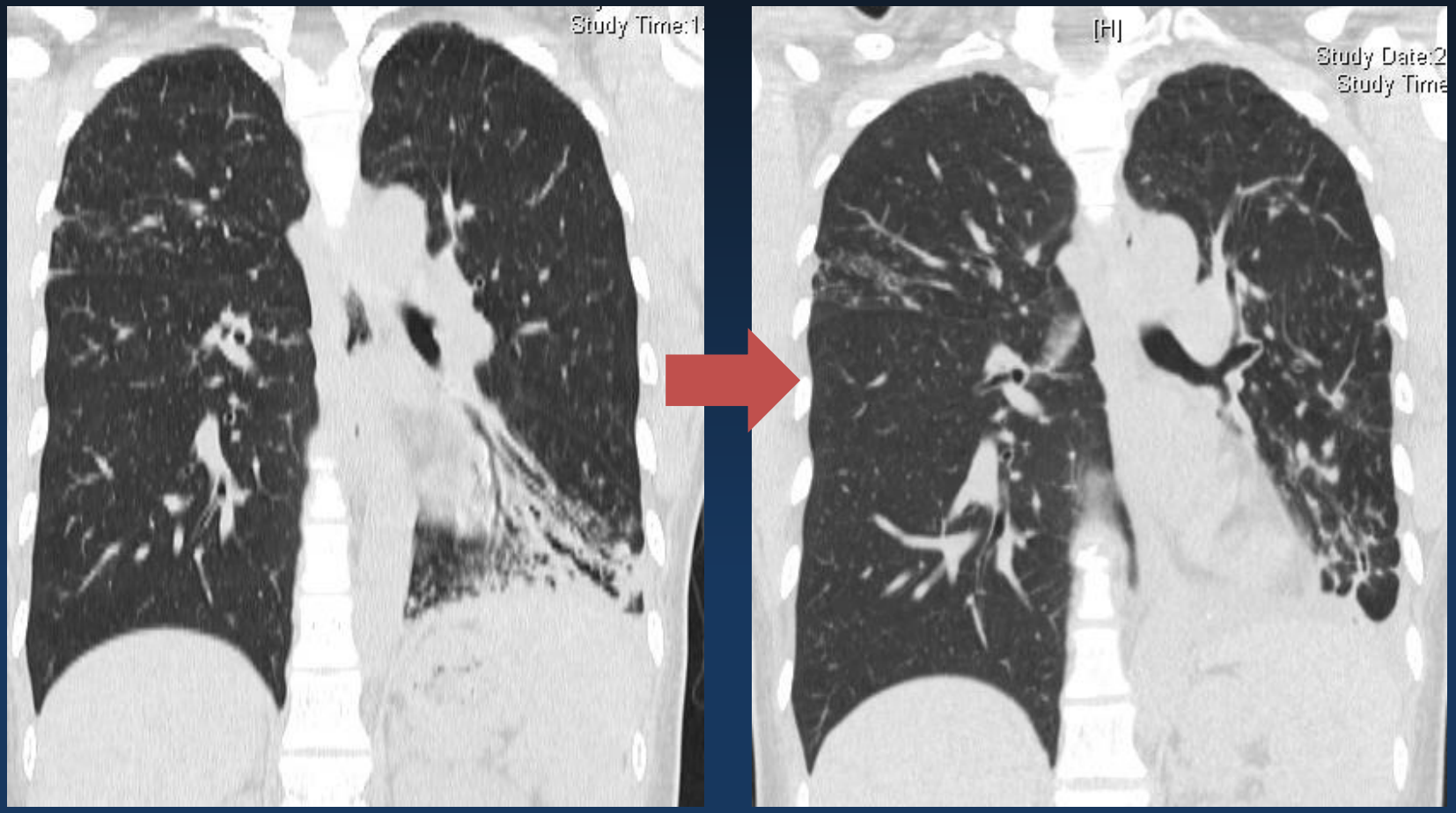


2020.08.03 starting antibiotics



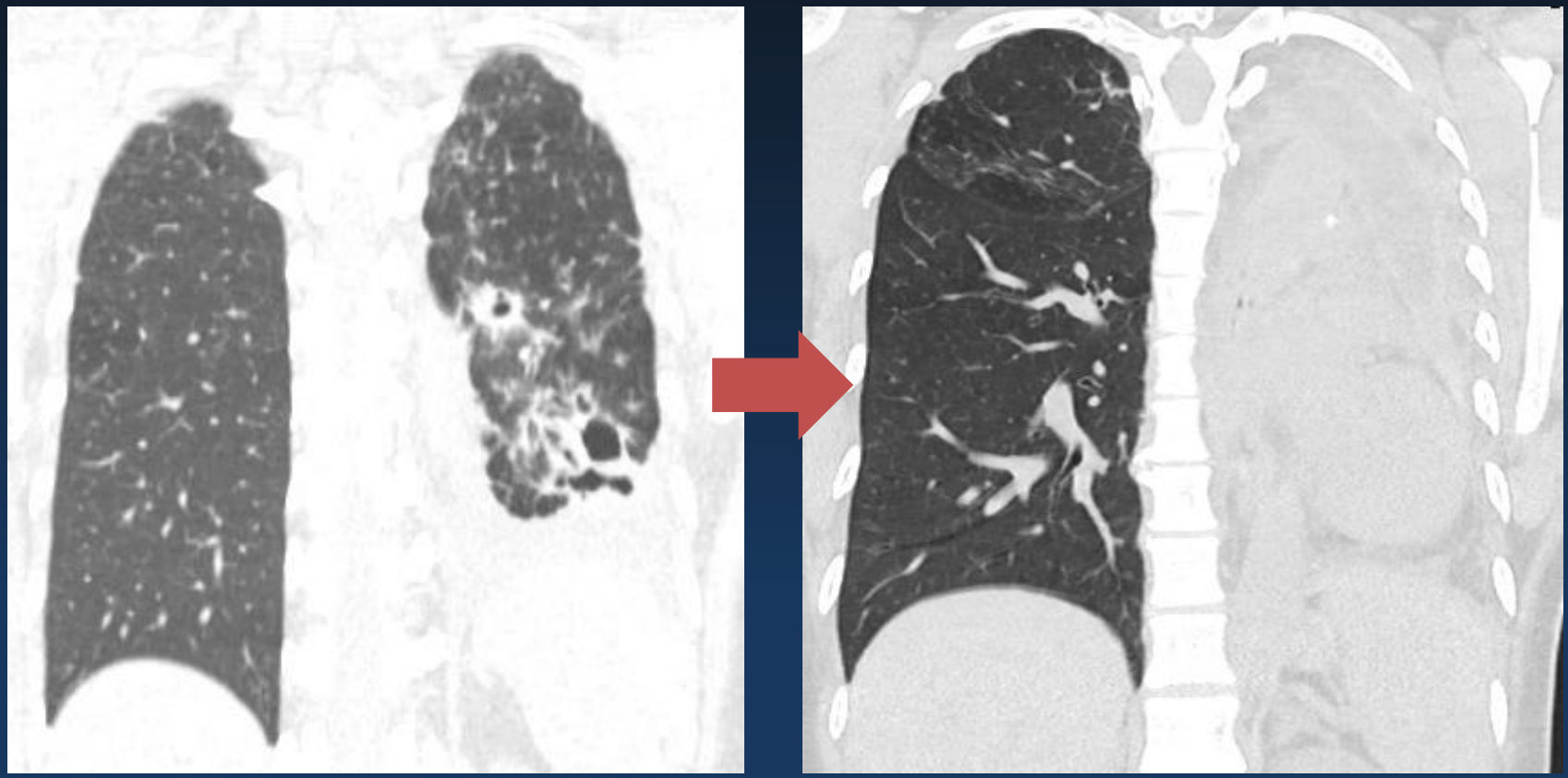
Recurrence even after repetitive lung resection

2007 *M. massiliense*, LLLobectomy + antibiotics



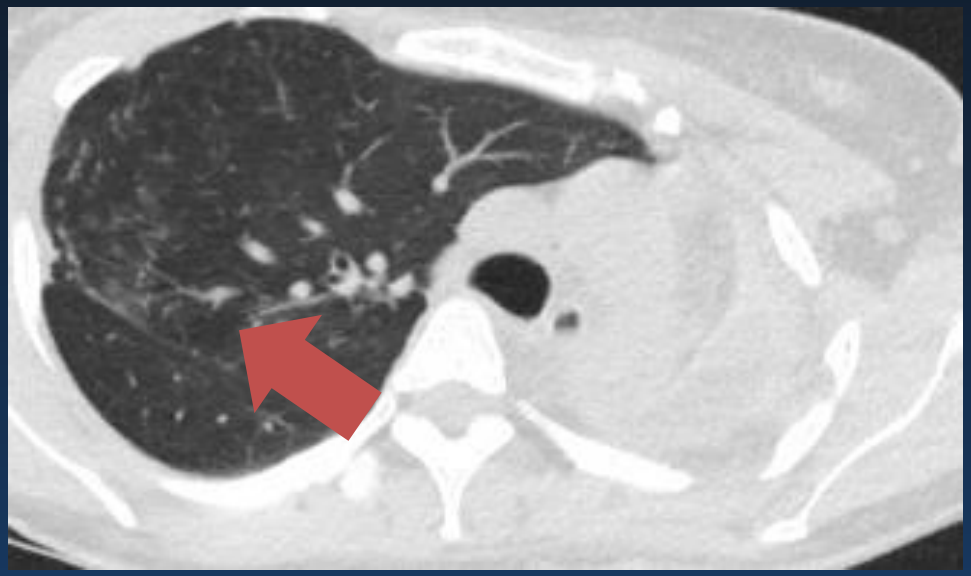
Recurrence even after repetitive lung resection

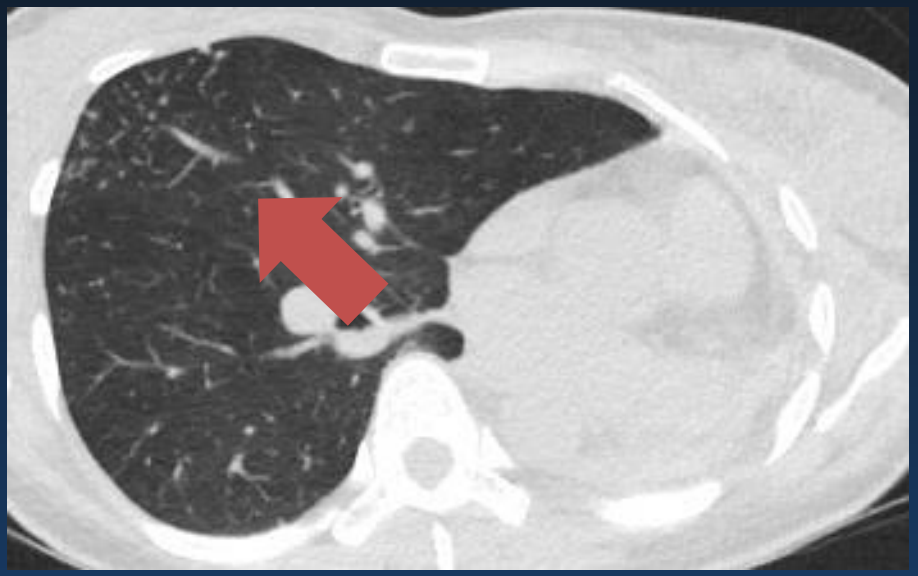
2015 *M. abscessus*, completion pneumonectomy left + antibiotics



Recurrence even after repetitive lung resection

2023 *M. avium*, re-infection





She said..

"I did everything the hospital and the doctors told me,

but why does it keep coming back? I won't get more treatment!!!"

Agenda

***M. avium* complex (MAC)**

- ALIS (amikacin liposome inhalation suspension)
- Three vs. Two regimen (macrolide/ethambutol ± rifampicin)
- Other agents (clofazimine, isoniazid etc.)

M. abscessus

- ALIS
- Intermittent multi-drug intravenous therapy (IMIT)

Clinical trial

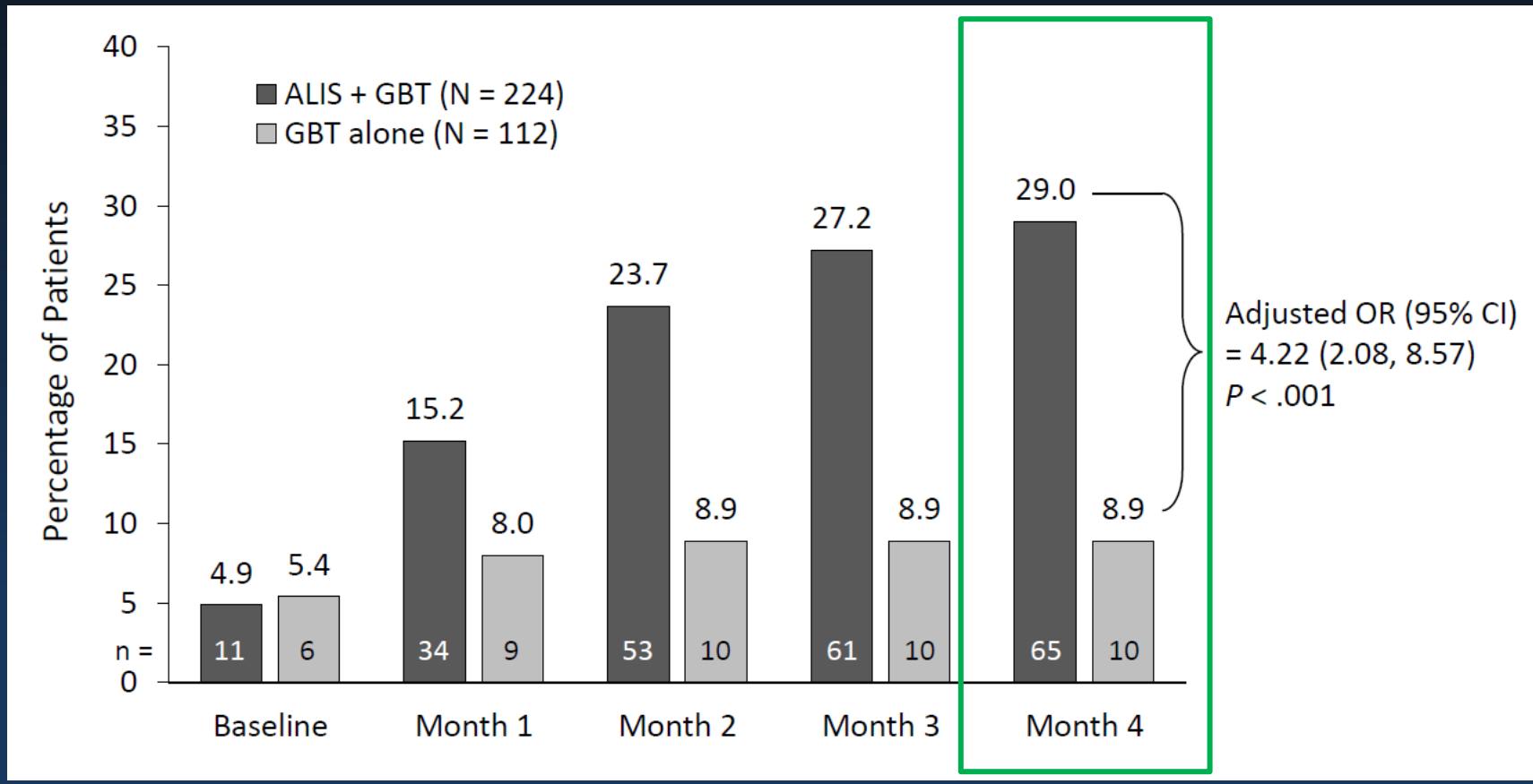
Survival benefit of antibiotics for NTM-PD

CONVERT STUDY

Amikacin liposome inhalation suspension, ALIS

- Adding ALIS in refractory MAC-PD -

Sputum culture conversion by study month



Am J Respir Crit Care Med 2018;198(12):1559-1569

Real world data of ALIS for MAC-PD

Early-phase adverse effects and management of ALIS for refractory MAC-PD

2021, Japan, Keio University Hospital

11 patients with refractory MAC-PD, **One month** outcome after adding ALIS

Case	Sex	Age	Species	MIC of CLA (μg/mL)	MIC of AMK (μg/mL)	Radiological Pattern	Prior Treatment	Total Treatment Duration Before ALIS (Year)	Drugs at ALIS Initiation	Sputum Culture Results Before ALIS Initiation	Sputum Culture Results 1 Month After ALIS Initiation
#1	F	56	*M.avium*	>32	4	NB	CLA, EB, RFP, RFB, EM, STFX	4.5	EB, RFP	+	+
#2	F	69	*M.avium*	4	1	NB+FC	CLA, EB, RFP, KM	19.8	CLA, EB, RFP	+	+
#3	M	76	*M.avium*	>32	16	NB	CLA, EB, RFP, EM	13.7	EB, RFP, EM	+	–
#4	F	69	*M.avium*	0.5	2	NB	CLA, EB, AZM	3.9	EB, AZM	+	–
#5	F	63	*M.avium*	>32	>16	NB+FC	CLA, EB, RFP, AMK div, AMK inh, STFX, LVFX	15.8	EB, RFP, STFX	+	+
#6	F	75	*M.avium*	0.5	16	NB	CLA, EB, RFP, RFB, AZM, AMK div, AMK inh	9.9	EB, AZM	+	–
#7	F	79	*M.avium*	>32	4	NB	CLA, EB, RFP	13.9	CLA, RFP	+	+
#8	F	64	*M.avium*	>32	>16	NB	CLA, EB, RFP, EM, SM, AMK div, AMK inh, STFX, SPFX, CPFX, ope	21.3	EB, RFP, EM, STFX	+	+
#9	M	61	*M.avium*	>32	8	NB	CLA, EB, RFP, EM, AMK div, STFX	7.3	EB, RFP, EM, STFX	+	+
#10	F	60	*M.avium*	2	8	NB+FC	CLA, EB, RFP, AZM, SM, CZM, LVFX	8.4	CLA, EB, RFP	+	+
#11	F	56	*M.intracellulare*	0.25	4	NB	CLA, EB, RFP, AZM	6.3	EB, AZM	+	+

3 patients were culture negative after 1 month of using ALIS

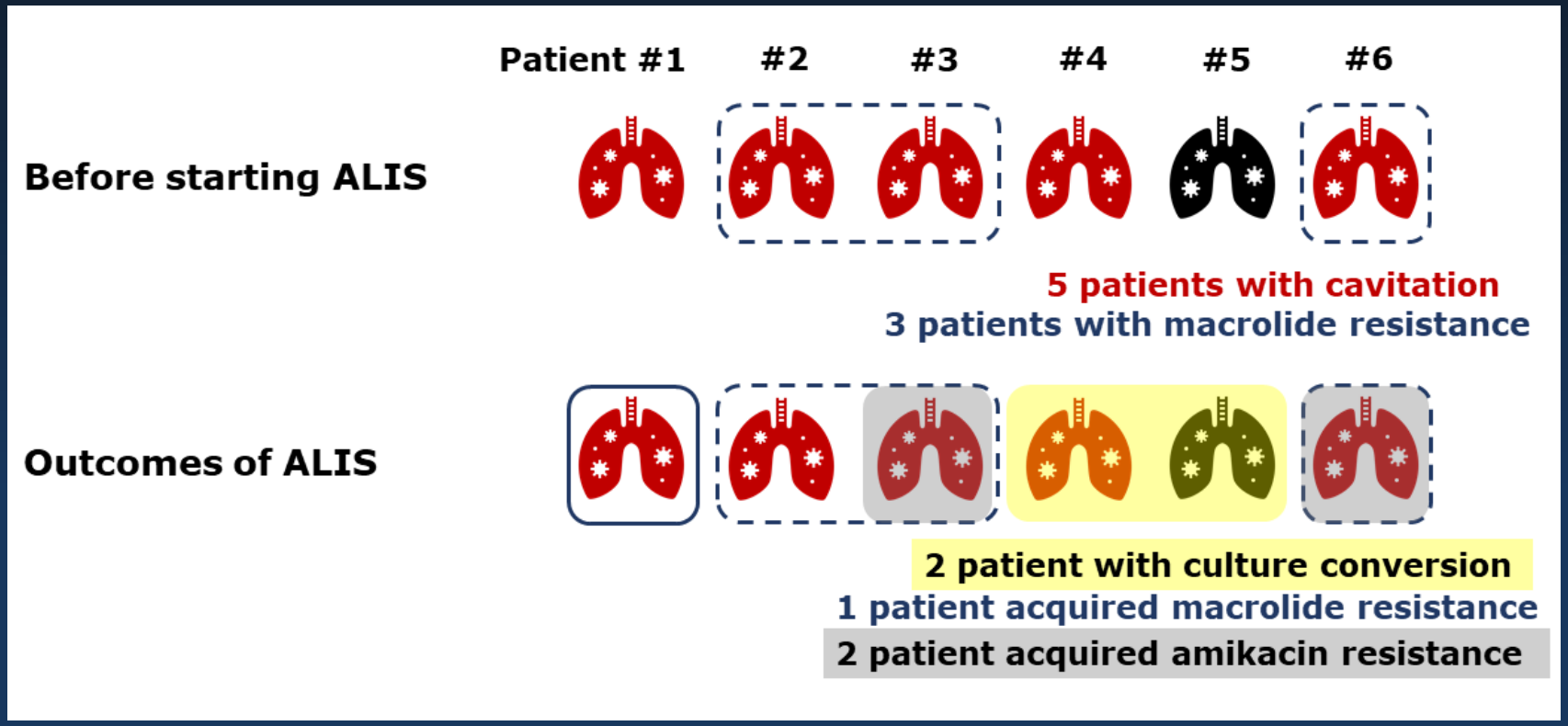
Infect Drug Resist 2022;15:4001-4011

Long-term outcome of ALIS for Refractory MAC-PD,

Samsung Medical Center

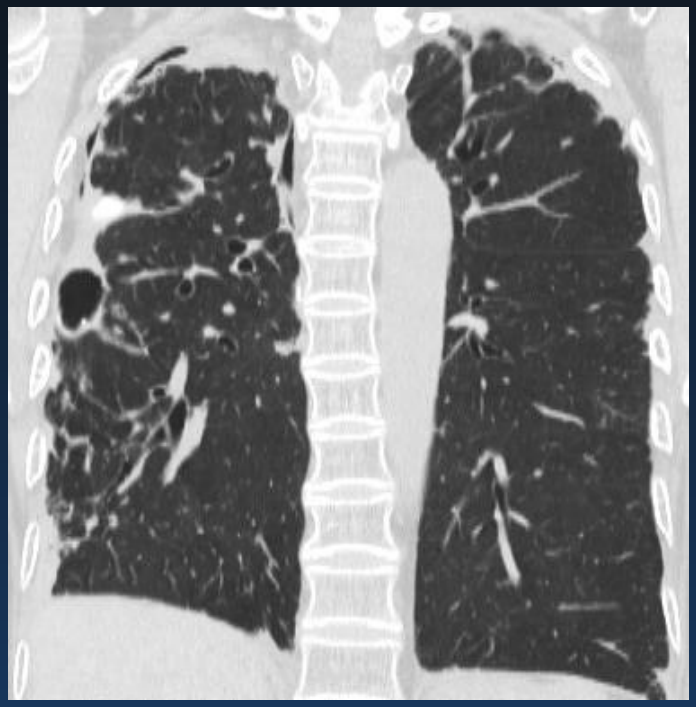
6 refractory MAC-PD patients, antibiotics > 2 years

Long-term outcomes after adding ALIS



Tuberc Respir Dis (Seoul) 2023: 10.4046/trd.2023.0120

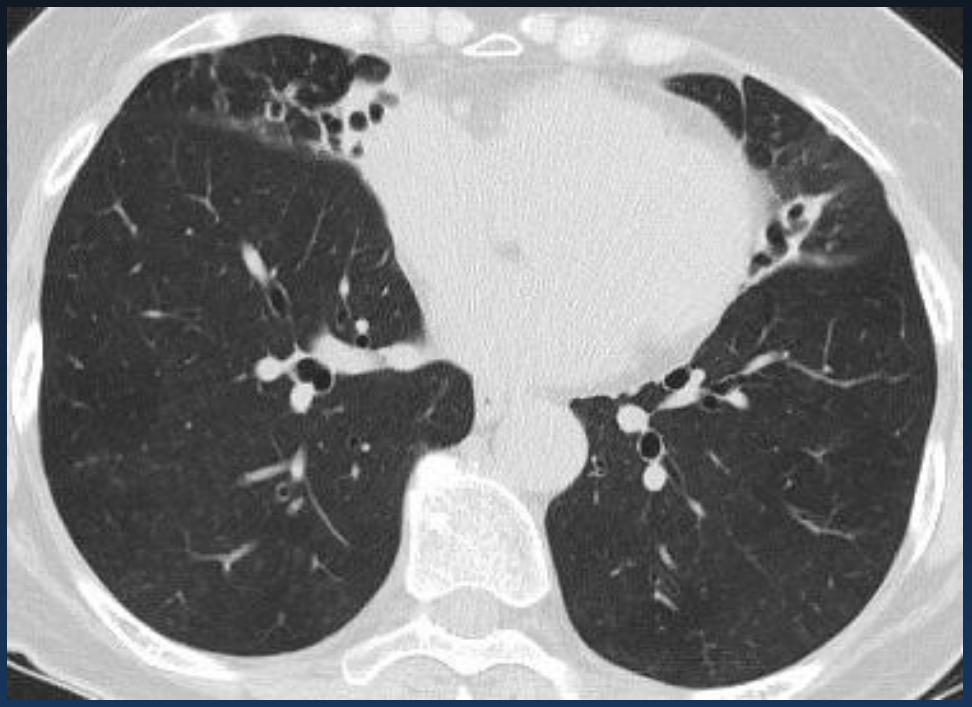
Microbiological cure after adding ALIS



M. intracellulare

ALIS duration, 10.3 months

Companion drugs, AZM EMB® MFX®



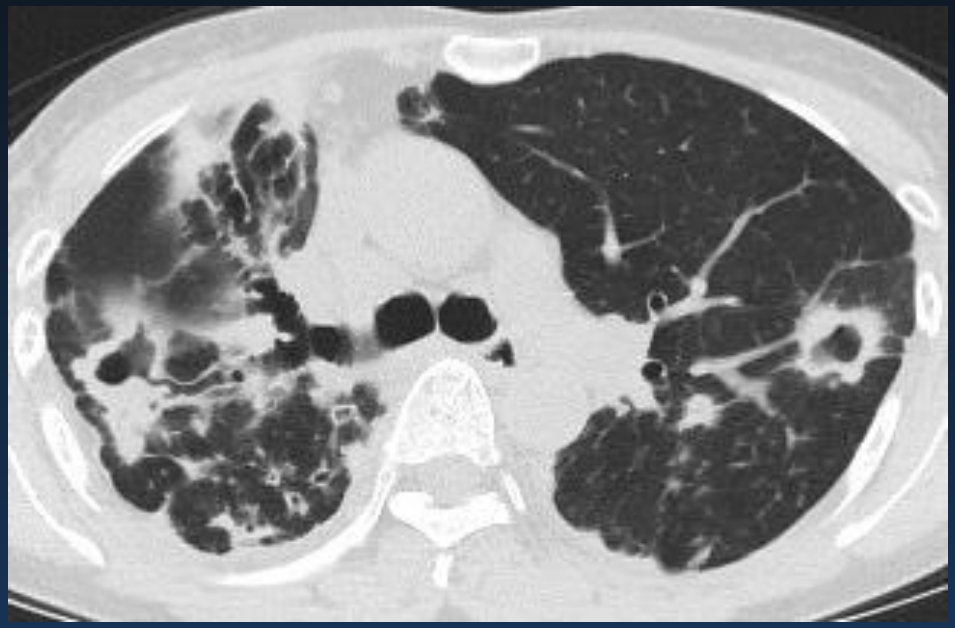
M. avium

ALIS duration, 2.8 months

Companion drugs, AZM EMB CFZ

Underlined antibiotics = resistance

Persistent positive culture after adding ALIS

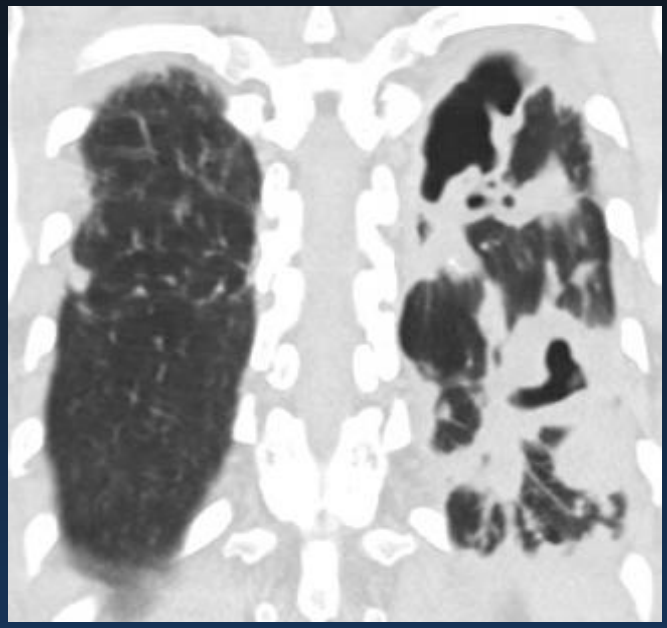


M. avium

ALIS duration, 13.3 months

Companion drugs, AZM EMB® RFB® MFX

Macrolide resistance after adding ALIS



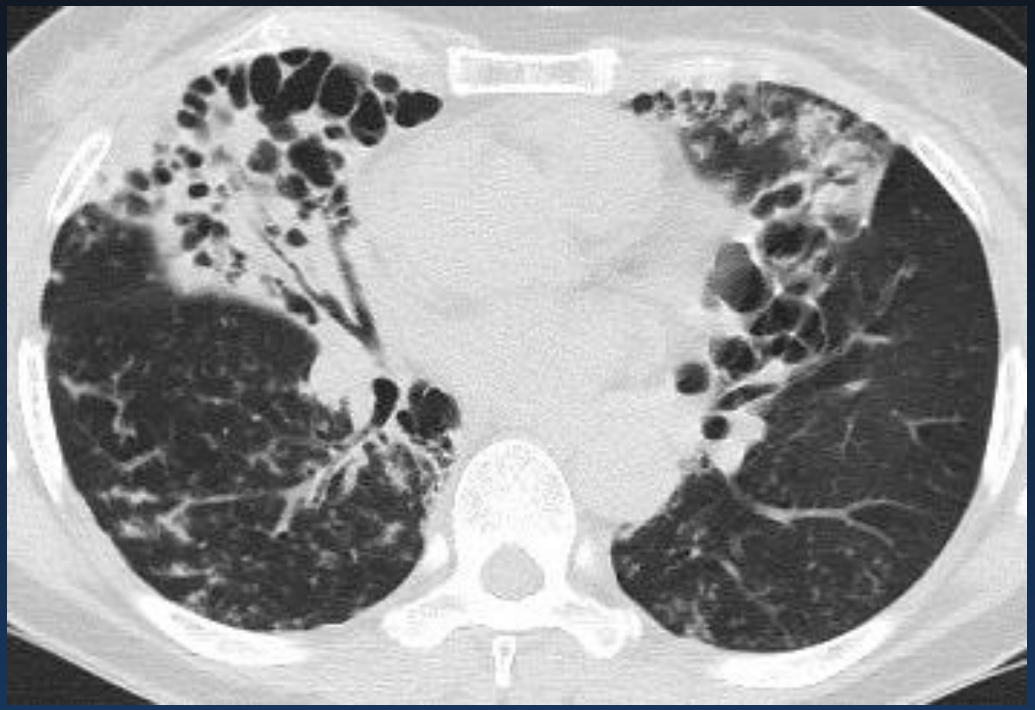
M. avium

ALIS duration, 13.2 months

Companion drugs, AZM® EMB® MFX CFZ

Underlined antibiotics = resistance

Persistent positive culture after adding ALIS

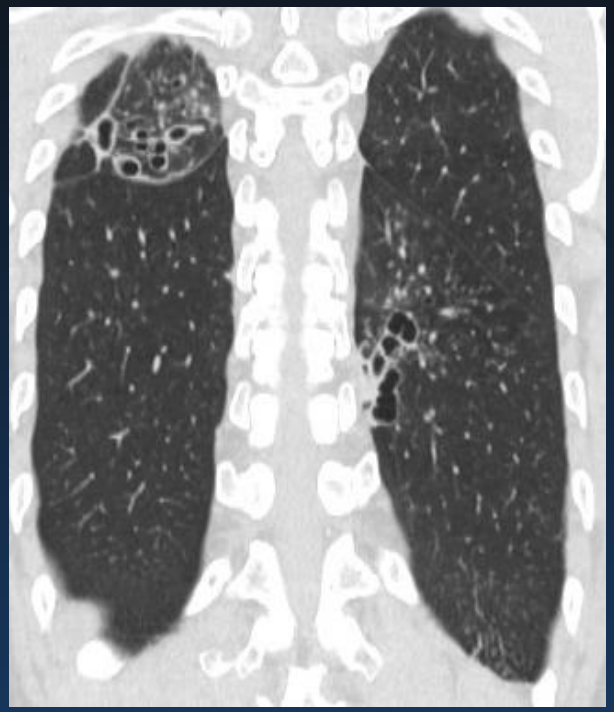


M. avium

ALIS duration, 7.1 months

Companion drugs, AZM® EMB® MFX® CFZ

Amikacin resistance after adding ALIS



M. avium

ALIS duration, 9.8 months

Companion drugs, AZM® EMB® RFB® MFX® CFZ

Amikacin resistance after adding ALIS

Underlined antibiotics = resistance

ALIS for Refractory MAC-PD, Samsung Medical Center

6 refractory MAC-PD patients, antibiotics > 2 years
Long-term outcomes after adding ALIS

The addition of ALIS to standard treatment improved microbiological or radiological responses in some patients. However, for patients with macrolide-resistant isolates or large cavity, the added benefit "may" be limited.

Tuberc Respir Dis (Seoul) 2023: 10.4046/trd.2023.0120

Two vs. Three regimen

Macrolide/Ethambutol ± Rifampicin

The Reasons for hesitation in using Rifampicin

- **Side effects**
  - Gastrointestinal disorders
  - Renal impairment
  - Hepatotoxicity, etc.
- **Reducing macrolide concentrations**
- **Insufficient MIC and clinical correlation data**

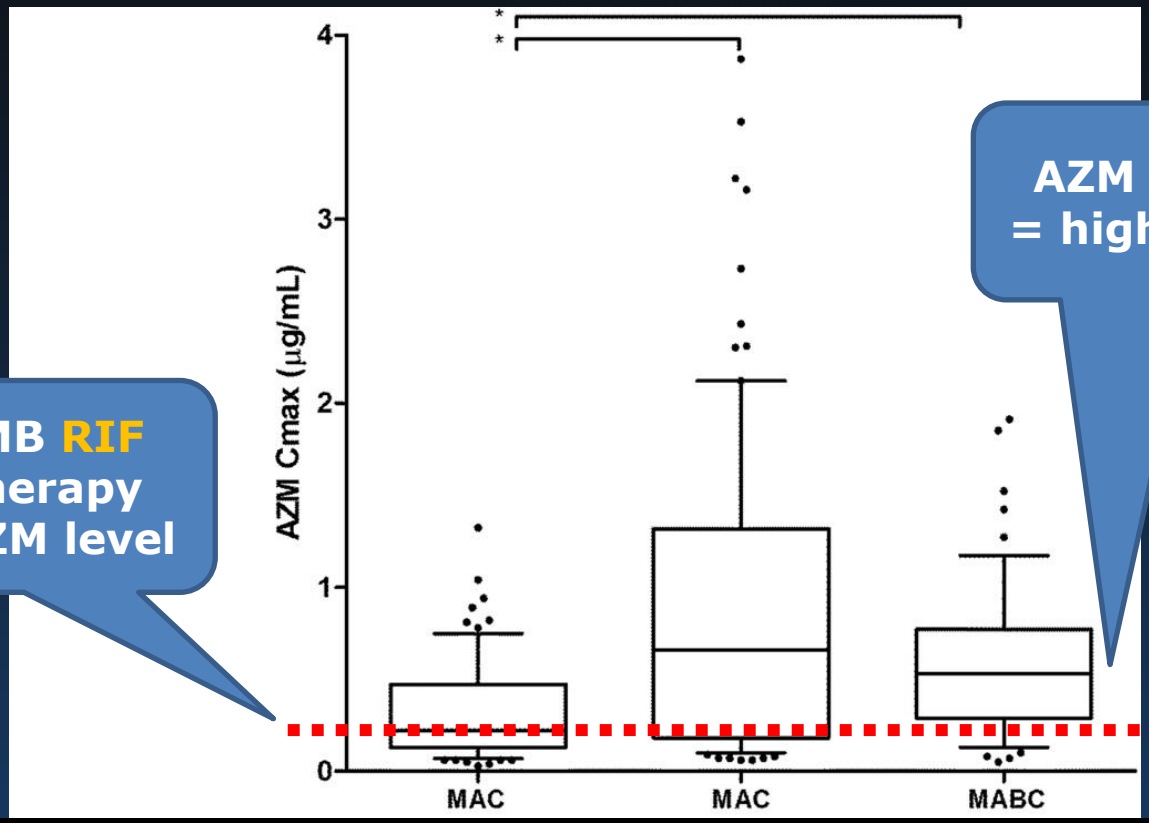
Does rifabutin (Rfb) prevent macrolide resistance?

A randomized, placebo-controlled study
AIDS with MAC bacteremia
CLR EMB "Rfb" vs. CLR EMB "placebo" at 16 week

	CLR EMB Rfb	CLR EMB placebo	p-value
Bacteriological response	44/70 (63%)	42/69 (61%)	0.810
Eradication	40/55 (73%)	37/51 (73%)	0.980
CLR resistance	1/44 (2%)	6/42 (14%)	0.055

Clin Infect Dis 1999;28(5):1080

Drug interactions, AZM and RIF



Higher AZM Cmax was associated with favorable microbiologic responses

*, Mann-Whitney *U* test with Bonferroni correction, $P < 0.001$.

†, Data are presented as medians (interquartile ranges).

Antimicrob Agents Chemother 2016;60(10):6076-83

CLR EMB vs. CLR EMB RIF
- Two vs. Three regimen -

Prospective study
119 MAC-PD patients, **CLR EMB vs. CLR EMB "RIF"**
12 months culture conversion (end-point)

	CLR EMB Daily (n = 60)	**CLR EMB RIF Daily (n = 59)**	**p-value**
Culture conversion			
intention-to-treat analysis	55%	41%	>0.05
per-protocol analysis	83%	75%	>0.05
Discontinuation	27%	37%	>0.05
CLR resistance	0%	0%	NA

Ann Am Thorac Soc 2014;11(1):23

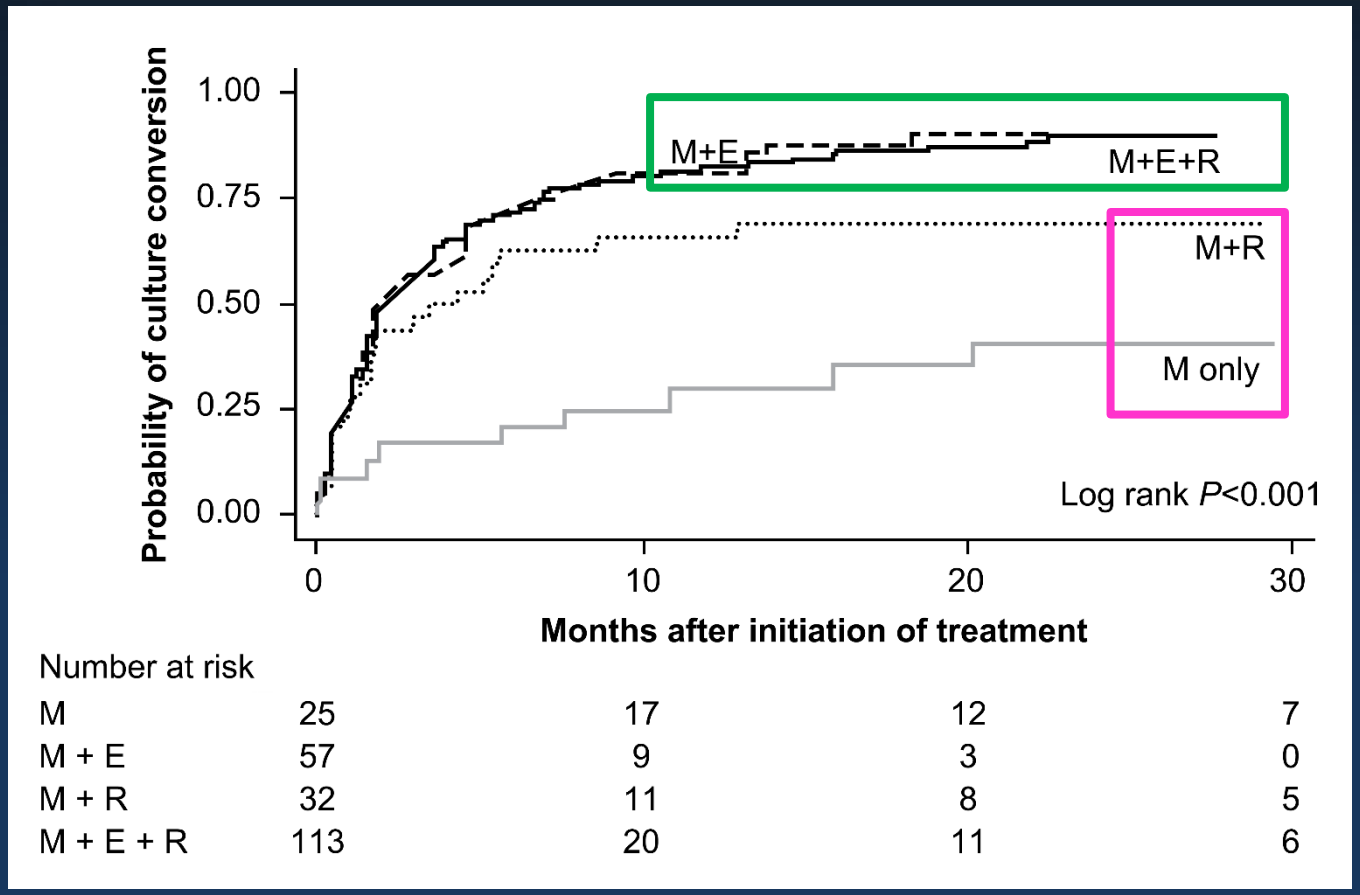
Previous regimens in MAC-PD patients who acquired macrolide resistance

	Griffith (2006)	Morimoto (2016)	Kadota (2016)	Moon (2016)
Patient no.	51	90	33	34
Previous treatment regimen				
macrolide monotherapy	55%	32%	18%	0%
macrolide + 1-drug			12%	
macrolide + RIF		26%		29%
macrolide + FQ	22%	7%		3%
macrolide + EMB		6%		3%
macrolide + 2-drugs	18%	30%	61%	65%
Treatment success	25%	11%	36%	15%

Am J Respir Crit Care Med. 2006 Oct 15;174(8):928
Ann Am Thorac Soc 2016;13:1904
BMC Infect Dis 2016;16:31
Antimicrob Agents Chemother 2016;60:6758

Conversion according to maintenance (≥6 mo) of EMB RIF in MAC-PD

Macrolide only	Macrolide and ethambutol	Macrolide and rifampicin	Macrolide, ethambutol, and rifampicin
n = 25	*n* = 58	*n* = 32	*n* = 122

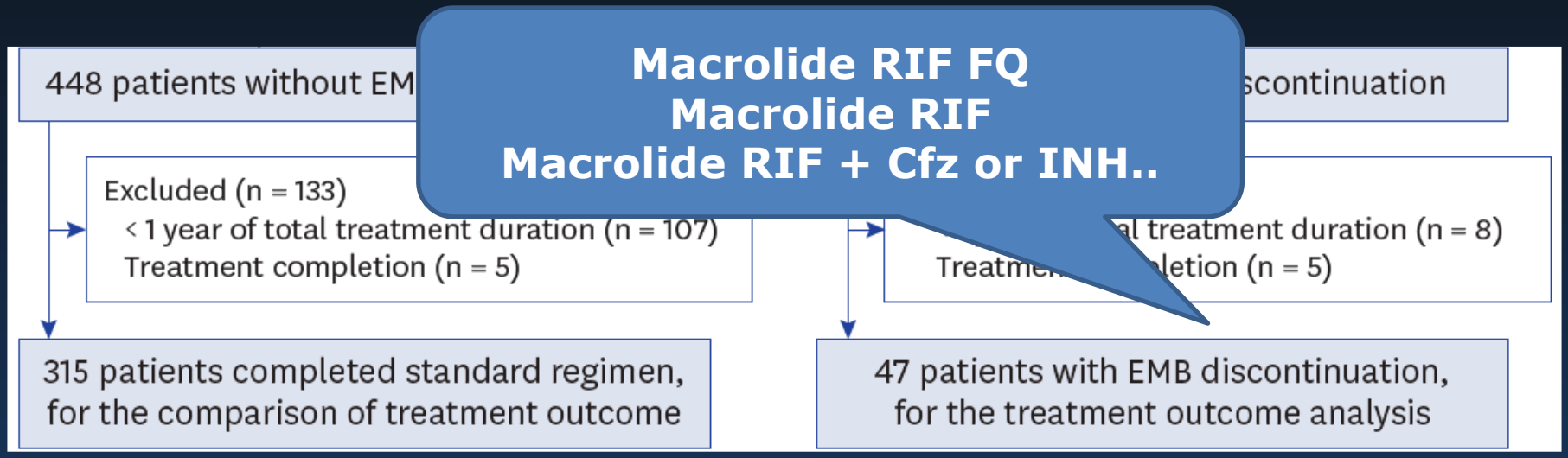


Number at risk

M	25	17	12	7
M + E	57	9	3	0
M + R	32	11	8	5
M + E + R	113	20	11	6

BMC Pulm Med 2019;19(1):212

Outcomes after discontinuation of EMB due to adverse effects in MAC-PD



After propensity matching, treatment failure rate

18.3% in standard vs. 29.6% in EMB discontinuation

Kwon et al. JKMS 2020;35(9):e59

Intermittent Treatment with Azithromycin and Ethambutol for Noncavitary *Mycobacterium avium* Complex Pulmonary Disease

Samsung Medical Center, South Korea, January 2011 and June 2017
Intermittent (thrice a week) AZIT EMB for 38 non-cavity MAC-PD
76% (29 of 38) achieved culture conversion

TABLE 1 Univariate and multivariate analyses for failure to achieve culture conversion after 12 months of treatment in 38 patients with noncavitary *Mycobacterium avium* complex pulmonary disease

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.0 (0.9–1.1)	0.306	22.4 (0.4–1188.4)	0.125
Male	3.1 (0.6–15.1)	0.168	0.9 (0.9–1.1)	0.986
Body mass index	1.0 (0.8–1.3)	0.924	0.8 (0.5–1.2)	0.279
Never smoker	1.4 (0.2–8.7)	0.737	0.1 (0.003–6.4)	0.303
Previous tuberculosis	0.3 (0.03–3.1)	0.328	0.2 (0.01–2.4)	0.178
Sputum AFB[a] smear positivity	9.2 (1.6–53.9)	0.014	26.7 (2.1–339.9)	0.011

sputum AFB smear (+), an independent factor for culture conversion failure

Antimicrob Agents Chemother 2019;64(1):e01787-19

MAC2v3 Pragmatic Clinical Trial

Home

Welcome to the MAC2v3 Study

A pragmatic clinical trial with the goal of improving patient care for pulmonary MAC disease.

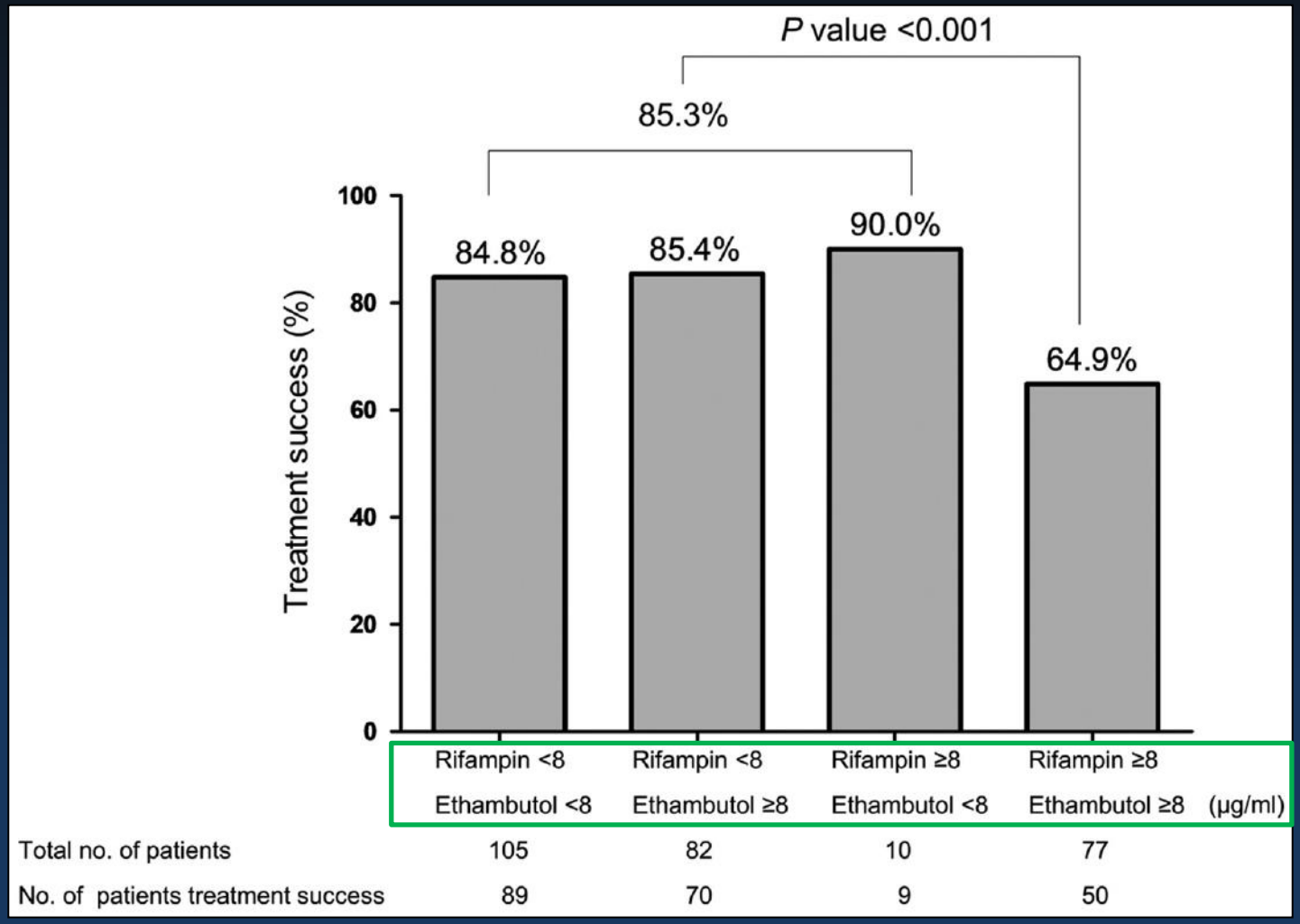
Over 300 subjects enrolled to-date!
Less than 200 subjects to go!

Study enrollment extended through Summer 2024

What are the clinical characteristics of patients who can achieve microbiological cure with only AZM EMB dual drug therapy?

MIC Values of EMB RIF, outcome in MAC-PD

- Asan Medical Center, South Korea -



Antimicrob Agents Chemother 2018 Sep 62:e00491

MIC Values of EMB RIF, outcome in MAC-PD

- Samsung Medical Center, South Korea -

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CLINICAL THERAPEUTICS

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Relationship between Resistance to Ethambutol and Rifampin and Clinical Outcomes in *Mycobacterium avium* Complex Pulmonary Disease

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Seong Mi Moon and Su-Young Kim contributed equally to this article. Author order was determined by the corresponding author.

ABSTRACT We evaluated the associations between the *in vitro* activities of ethambutol and rifampin and clinical outcomes of *Mycobacterium avium* complex (MAC) pulmonary disease (PD). Among 158 patients with MAC-PD, there was no relationship between high MICs for ethambutol and/or rifampin and treatment failure for MAC-PD. Ethambutol and rifampin resistance was common among MAC isolates (rates of 87% and 59%, respectively), but mutations in *embB*, *rpoB*, and *rpoC* were rare, with detection in only 4% of the drug-resistant MAC isolates.

KEYWORDS *Mycobacterium avium* complex, ethambutol, rifampin, MIC, outcome

Antimicrob Agents Chemother 2022;66(4):e0202721

MIC Values of EMB RIF, outcome in MAC-PD

- Samsung Medical Center, South Korea -

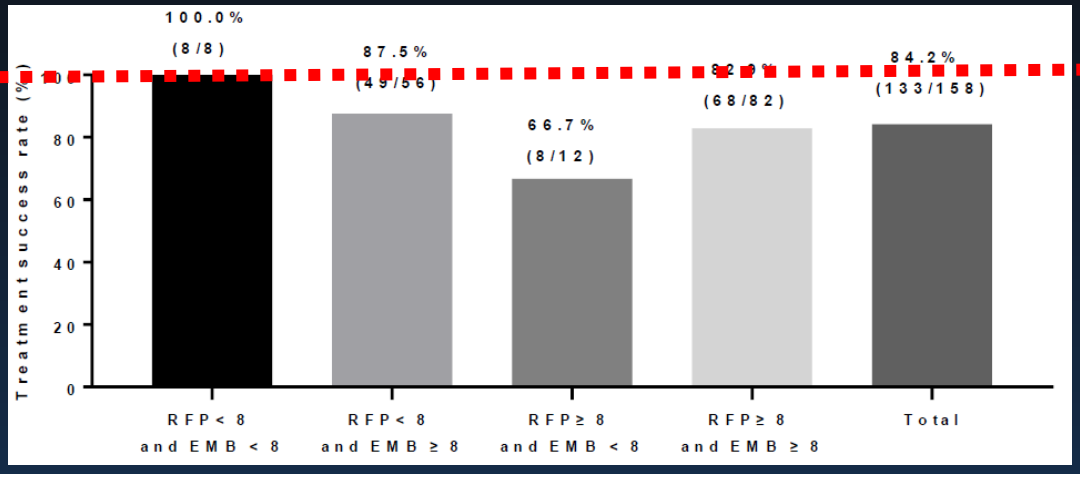

TABLE 2 Treatment outcomes at 12 months and at the end of treatment according to ethambutol and rifampin MICs of pretreatment isolates from 158 MAC-PD patients

	Ethambutol			Rifampin		
MIC (μg/mL)	No. (%) of patients	No. with culture conversion at 12 mo after treatment/ total no. (%)	No. with treatment success with microbiological cure/total no. (%)	No. (%) of patients	No. with culture conversion at 12 mo after treatment/total no. (%)	No. with treatment success with microbiological cure/total no. (%)
0.5				1 (1)	1/1 (100)	1/1 (100)
1	1 (1)	1/1 (100)	1/1 (100)	5 (3)	4/5 (80)	4/5 (80)
2	2 (1)	2/2 (100)	2/2 (100)	27 (17)	24/27 (89)	26/27 (96)
4	17 (11)	15/17 (88)	13/17 (77)	31 (20)	26/31 (84)	26/31 (84)
8	24 (15)	18/24 (75)	17/24 (71)	48 (30)	41/48 (86)	39/48 (81)
16	35 (22)	29/35 (83)	29/35 (83)	28 (18)	25/28 (89)	24/28 (86)
32	21 (13)	20/21 (95)	20/21 (95)	18 (11)	12/18 (67)	13/18 (72)
>32	58 (37)	48/58 (83)	51/58 (88)			

Antimicrob Agents Chemother 2022;66(4):e0202721

Reasons for Discrepancy Between AMC and SMC Data

- Unlike the AMC analysis, SMC data was reported to be (statistically) unrelated to the MIC level of EMB and RIF in terms of treatment outcomes.
- However, in SMC data, although not statistically significant, there was a tendency for lower treatment outcomes as the MIC level of EMB and RIF increased.
- These results suggest that in SMC patients, the overall regimen's effectiveness (especially high-dose macrolides) may played a role.
- Further studies with a larger number of patients are needed.

Optimal dosage of ethambutol ?

ORIGINAL PAPER

Low-dosage ethambutol, less than 12.5 mg/kg/day, does not worsen the clinical outcomes of pulmonary *Mycobacterium avium* and *Mycobacterium intracellulare* disease: a retrospective cohort study

Fumiya Watanabe[1,2] · Shota Kaburaki[3] · Koji Furuuchi[3] · Fumiko Uesugi[3] · Keiji Fujiwara[3] · Yoshiaki Tanaka[3] · Takashi Yoshiyama[3] · Yuji Shiraishi[3] · Atsuyuki Kurashima[3] · Ken Ohta[3] · Kazuhiko Hanada[1] · Kozo Morimoto[3,4]

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Abstract

Objectives Multidrug chemotherapy is recommended for treating pulmonary *Mycobacterium avium* and *Mycobacterium intracellulare* disease. Although ethambutol has been demonstrated to inhibit macrolide resistance, the ethambutol dosage is sometimes decreased due to concerns about optic neuropathy. We aimed to assess whether lower ethambutol doses impact treatment outcomes.

Methods Patients treated over 12 months between 2016 and 2020 were collected retrospectively. Clinical outcomes, including negative culture conversion, microbiological cure, adverse events, resistance to macrolides, and recurrence, were compared according to daily ethambutol dosage.

Results Among 146 patients, 42 were treated with ethambutol dosages over 12.5 mg/kg/day, and 104 were treated with lower dosages. Negative culture conversion was achieved for 125 patients, and 90 patients achieved microbiological cure. Recurrence was identified in 16 patients who achieved microbiological cure. No macrolide resistance was observed, and no significant difference was observed in the percentage of negative culture conversion ($P = 1.00$) or microbiological cure ($P = 0.67$) between the high- and low-dosage ethambutol groups. Sputum smear positivity was associated with a lower adjusted odds ratio (aOR) of negative culture conversion (aOR: 0.48, 95% CI: 0.29–0.80). A lower aOR of microbiological cure was independently associated with sputum smear positivity (aOR: 0.52, 95% CI: 0.37–0.74) and with the use of an intermittent regimen (aOR: 0.60, 95% CI: 0.41–0.87). Daily ethambutol dosage was not identified as a prognostic factor for any of the outcomes. Optic neuropathy was observed in 7.1% of the high-dose ethambutol group and 1.0% of the low-dosage ethambutol group ($P = 0.07$).

Conclusion An ethambutol dosage of 12.5 mg/kg/day or less in guideline-based chemotherapy may reduce optic neuropathy without worsening clinical outcomes.

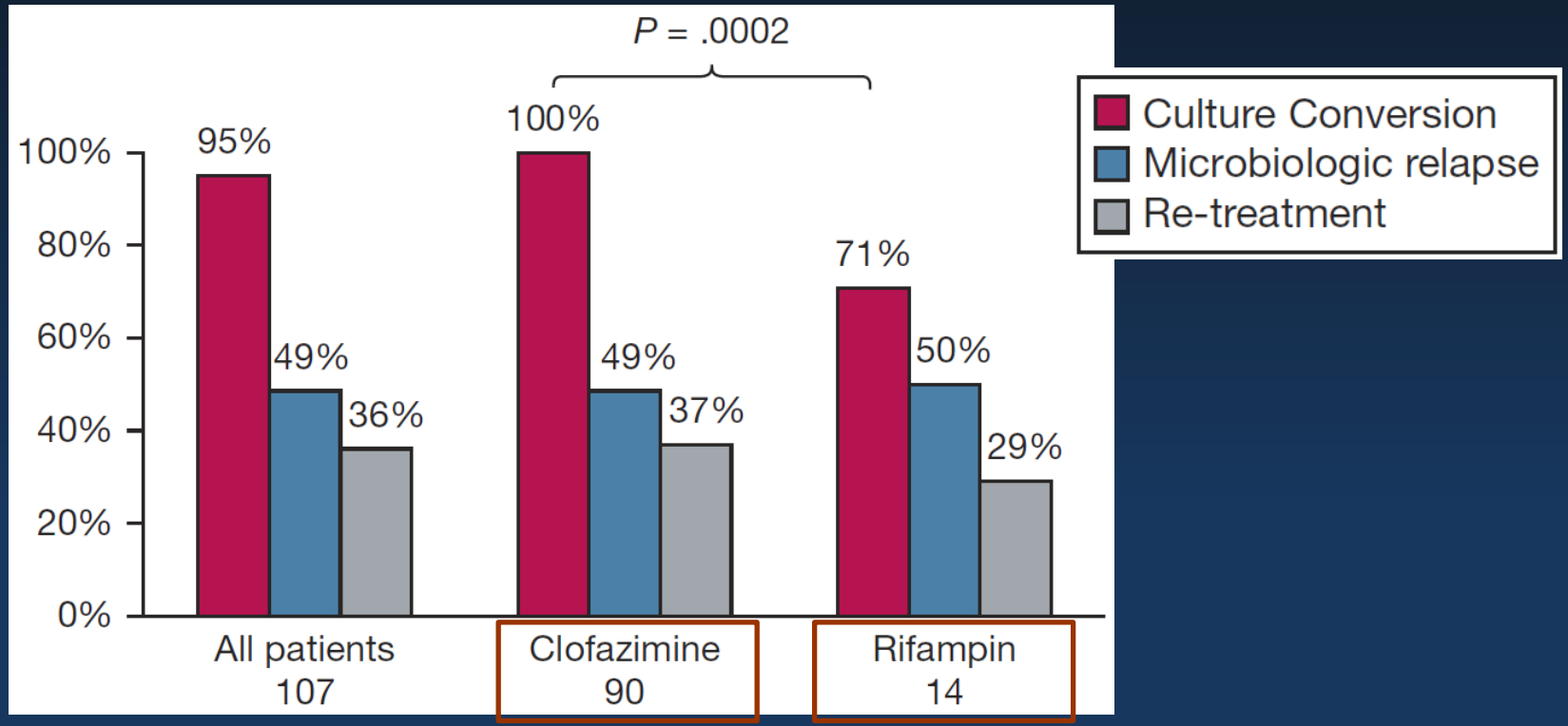
Infection 2022;50(4):879-887

Other agents

Clofazimine Isoniazid

Clofazimine vs. RIF in MAC-PD

University of Calgary, Canada
107 MAC-PD patients
"Macrolide EMB Clofazimine" vs. "Macrolide EMB RIF"



Chest 2016 May;149(5):1285

Minimal Inhibitory Concentration of Clofazimine Among Clinical Isolates of Nontuberculous Mycobacteria and Its Impact on Treatment Outcome

Nakwon Kwak, MD; Jake Whang, PhD; Jeong Seong Yang, MS; Taek Soo Kim, MD; Sung A. Kim, RN; and Jae-Joon Yim, MD

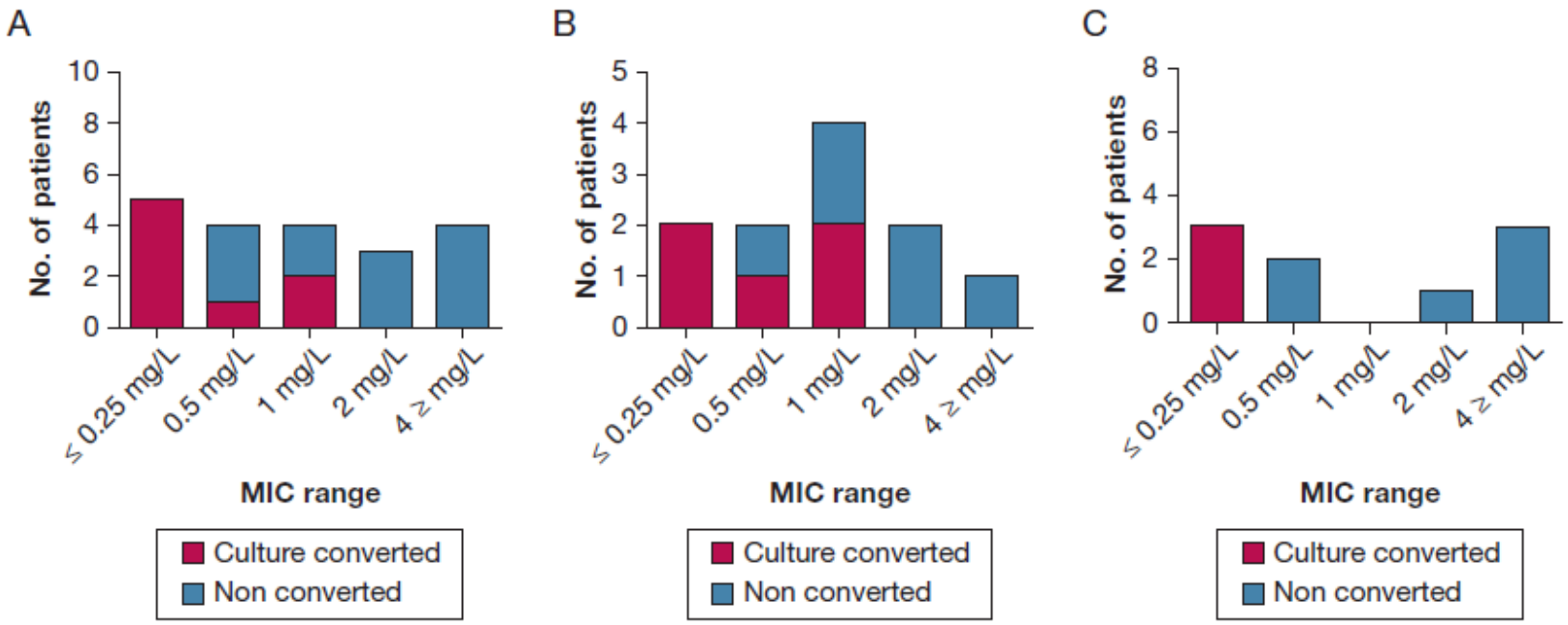


Figure 2 – *The number of patients who achieved culture conversion and whose conditions failed culture conversion according to minimal inhibitory concentration range. A, Total. B, Mycobacterium avium complex. C,* Mycobacterium abscessus.

Chest 2020;S0012-3692(20)32059-6

Journal of *Clinical Medicine*

MDPI

Article

Outcomes of Inhaled Amikacin and Clofazimine-Containing Regimens for Treatment of Refractory *Mycobacterium avium* Complex Pulmonary Disease

Adding Clofazimine + Inhaled non-lipo Amikacin =

29% (15 of 52) favorable outcome

in refractory MAC-PD

Abstract: Limited data are available regarding optimal treatment for refractory *Mycobacterium avium* complex-pulmonary disease (MAC-PD). We evaluated outcomes of inhaled amikacin (AMK) with clofazimine (CFZ) regimens as an add-on salvage therapy for refractory MAC-PD. We retrospectively analyzed 52 patients with refractory MAC-PD, characterized by persistently positive sputum cultures despite >6 months of treatment. Thirty-five (67%) patients had *M. intracellulare*-PD, and 17 (33%) patients had *M. avium*-PD. Twenty-seven (52%) patients received the salvage therapy for ≥12 months, whereas 25 (48%) patients were treated for <12 months due to adverse effects or other reasons. Seventeen (33%) patients had culture conversion: 10 (10/27) in the ≥12-month treatment group and seven (7/25) in the <12-month treatment group ($p = 0.488$). Microbiological cure, defined as maintenance of culture negativity, was achieved in 12 (23%) patients; six (6/12) with accompanying symptomatic improvement were considered to have reached cure. Clinical cure, defined as symptomatic improvement with <3 consecutive negative cultures, was achieved in three (6%) patients. Overall, 15 (29%) patients achieved favorable outcomes, including microbiological cure, cure, and clinical cure. Inhaled AMK with CFZ may provide favorable outcomes in some patients with refractory MAC-PD. However, given the adverse effects, more effective strategies are needed to maintain these therapeutic regimens.

Isoniazid ? for refractory MAC-PD ?

- 2017 BTS guideline vs. Expert review -

SECTION 12A: WHAT ANTIBIOTIC REGIMEN SHOULD BE USED TO TREAT MAC-PULMONARY DISEASE?

Recommendations

- Clarithromycin-sensitive MAC-pulmonary disease should be treated with rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (three times per week) or daily oral regimen. The choice of regimen should be based on the severity of disease (as defined in table 3) and treatment tolerance. (Grade D)
- An intermittent (three times per week) oral antibiotic regimen should not be used in individuals with severe MAC-pulmonary disease (as defined in table 3) or in individuals with a history of treatment failure. (Grade D)
- An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe MAC-pulmonary disease (as defined in table 3). (Grade D)
- Clarithromycin-resistant MAC-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a

Table 3
Building a treatment regimen for macrolide-resistant *Mycobacterium avium* complex pulmonary disease

Action	Why?
Stop the macrolide	Does not improve outcome
Continue ethambutol	Improves outcome
Change rifampin to rifabutin	Slightly more in vitro activity with rifabutin
Add amikacin (IV), transit[illegible]nhaled	Improves outcome when combined with surgery
Add another drug(s)	Have varying degrees of in vitro activity and tolerance
Do not add isoniazid	Minimal in vitro activity—more risk than benefit
Do not add a fluoroquinolone	Minimal in vitro activity and associated with worse outcomes
Consider surgical resection	Improves outcomes but not for everyone
Consult an expert	Provides invaluable knowledge and experience

2017 British Thoracic Society guidelines
Charles L. Daley 2023 Clin Chest Med

A study of isoniazid in MAC-PD treatment

Original articles

First randomised trial of treatments for pulmonary disease caused by *M avium intracellulare*, *M malmoense*, and *M xenopi* in HIV negative patients: rifampicin, ethambutol and isoniazid versus rifampicin and ethambutol

Research Committee of the British Thoracic Society

Table 2 Results during and after treatment

	M malmoense (n=106)		*MAC (n=75)*		*M xenopi (n=42)*		*All three species*		*Total*
	RE	*REH*	*RE*	*REH*	*RE*	*REH*	*RE*	*REH*	
No entered	52	54	37	38	22	20	112	111	223
No deviated from protocol	15^{1D}	12^{1D}	6	8	3	5	24^{1D}	25^{1D}	49^{2D}
No of deaths from all causes	12^{1W}	15^{1R1W}	9^{3F}	14^{2F1R}	11^{1F}	13^{1F}	32^{4F1W}	42^{3F2R1W}	74^{7F2R2W}
No died because of mycobacteria	1	3	0	3	0	3	1*	9*	10
No of failures of treatment and relapses	3 + 3 (6)	0 + 5 $(5)^{1D}$	7^{3D} + 8 (15)†	4^{2D} + 2^{1D} (6)	2^{1D} + 2 (4)	1^{1D} + 0 (1)	12^{4D} + 13 (25)‡	5^{3D} + 7^{1D} (12)‡	37^{9D}
No who completed treatment as allocated and were alive and cured at 5 years	20	24	10	13	5	2	35	39	74

*p = 0.018 (Fisher's exact test); †χ^2=4.5; p=0.033; ‡χ^2=4.5; p=0.033
Superscripts show patients represented in other categories: W = deviated from protocol; F = failure of treatment; R = relapse; d = death
RE = rifampicin + ethambutol; REH = rifampicin + ethambutol + isoniazid.

Small number of patients without macrolide

Thorax 2001;56(3):167-72

ALIS for *M. abscessus*-PD

ALIS for *M. abscessus* pulmonary disease

[Chest Infections Original Research]

CHEST

Open-Label Trial of Amikacin Liposome Inhalation Suspension in *Mycobacterium abscessus* Lung Disease

ALIS + background multidrug regimen for 12 months

15 of 30 patients (50%) demonstrated culture conversion

10 of 15 patients (67%) sustained conversion through month 12

6 of the 33 patients (18%) demonstrated mutational amikacin resistance

microbials. *M abscessus* treatment success is low in the presence of macrolide resistance.

RESEARCH QUESTION: Does treatment with amikacin liposome inhalation suspension (ALIS) improve culture conversion in patients with *M abscessus* pulmonary disease who are treatment naive or who have treatment-refractory disease?

Chest 2023;S0012-3692(23)00807-3

ALIS for *M. abscessus* pulmonary disease

41 CF or non-CF patients with : subspecies *abscessus, massiliense, bolletii*

Good outcome 25 (61%)

= microbiological cure (8) + clinical cure (7) + cure (13)

Safety and Outcomes of Amikacin Liposome Inhalation Suspension for *Mycobacterium abscessus* Pulmonary Disease

A NTM-NET study

To the Editor:

Mycobacterium abscessus is an opportunistic pathogen notorious for its antibiotic resistance and poor treatment outcomes.[1] Treatment regimens for *M abscessus* pulmonary disease consist of an intensive phase of 2 to 3 months of IV antibiotics (including amikacin, imipenem or cefoxitin, and tigecycline) combined with oral drugs (including clofazimine, linezolid, azithromycin). The continuation phase consists of two or three oral antibiotics, preferably with proven in vitro activity, and inhaled amikacin.[1,2]

Amikacin liposome inhalation suspension (ALIS) allows for better biofilm and macrophage penetration[3] and is likely more effective than inhalation of the IV solution of the drug. We aimed to assess the safety and outcomes of compassionate use of ALIS in *M abscessus* pulmonary disease.

Chest 2022;162(1):76-81

ALIS for *M. abscessus* pulmonary disease

Open Forum Infectious Diseases

MAJOR ARTICLE

Amikacin Liposomal Inhalation Suspension in the Treatment of *Mycobacterium abscessus* Lung Infection: A French Observational Experience

Retrospective observational cohort study, 26 patients, France

Culture conversion = 54% (14/26)

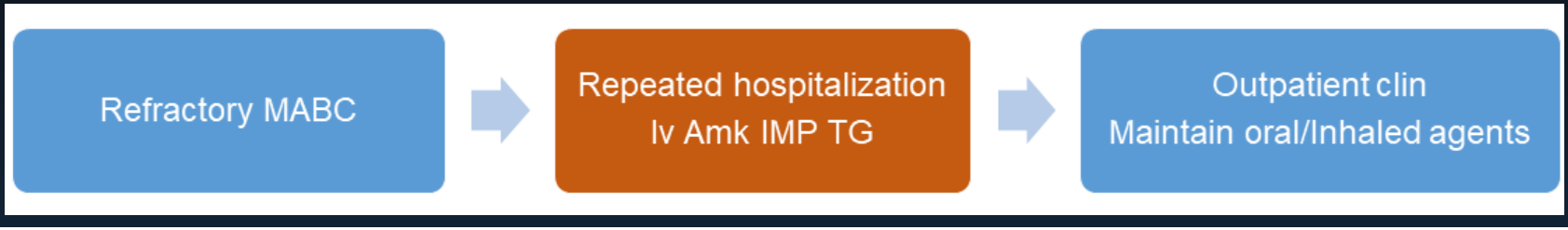
Average treatment duration of 10 months

Institut National de la Santé et de la Recherche Médicale (INSERM), Centre National de la Recherche Scientifique UMR 9004, Université Montpellier, Montpellier, France, [7]Institut de Recherche en Infectiologie de Montpellier, Institut National de la Santé et de la Recherche Médicale (INSERM), Montpellier, France, [8]Quantif-LITIS Laboratory EA 4108, Rouen University, Rouen, France, [9]Respiratory Diseases Department, University Hospital Centre Montpellier, Montpellier, France, [10]PhyMedExp, Institut National de la Santé et de la Recherche Médicale (INSERM) U1046, Université Montpellier, Montpellier, France, [11]Université Paris-Saclay, Hopital Raymond Poincaré, GHU–AP-HP, Paris, France, [12]Service de Microbiologie, Garches UVSQ, Institut National de la Santé et de la Recherche Médicale (INSERM), Montigny le Bretonneux, France, [13]PhyMedExp, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre National de la Recherche pour la Santé (CNRS), Montpellier, France, [14]Paediatric and Respiratory Departments, University Hospital Centre Montpellier, CF Center, Montpellier, France, [15]Laboratoire de bactériologie, University Hospital Centre Montpellier, MIVEGEC, IRD-CNRS-UM, Montpellier, France, [16]Service de Pneumologie, AP-HP, Hôpital Saint-Louis, Paris, France, [17]Biostatistics and Clinical Epidemiology Research Team, Université Paris Diderot, Sorbonne Paris Cité, U1153 CRESS, Paris, France, [18]Centre Hospitalier Universitaire Pointe-à-Pitre Abymes, Pointe-a-Pitre, Guadeloupe, France, [19]Pharmacy Department, University Hospital Centre Montpellier, Montpellier, France, [20]Respiratory Department, Centre Hospitalier Universitaire (CHU) Amiens-Picardie, Avenue Laënenc, Amiens, France, [21]Amiens University, EA 4294 AGIR, Amiens, France, [22]Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, AP-HP, Paris, France, [23]Centre d'Immunologie et des Maladies Infectieuses, Sorbonne Université, Paris, France, [24]Pneumologie et Transplantation Pulmonaire, Hopital Foch, Suresnes, France, and [25]Pneumology Department, Hôpital Foch, Suresnes, France

Open Forum Infect Dis 2022;9(10):ofac465

Intermittent Multi-drug Intravenous Therapy

- Samsung Medical Center-



Results: Of the 36 patients, 26 (72%) had M. abscessus subspecies abscessus (herein, M. abscessus)-PD, and 10 (28%) had M. abscessus subspecies massiliense (herein, M. massiliense)-PD. The median number of hospitalizations for IMIT was two (interquartile range [IQR] 1-3) for M. abscessus-PD patients and one (IQR 1-2) for M. massiliense-PD patients. At least one negative culture and culture conversion were observed in 62% and 12% of M. abscessus-PD patients, and in 80% and 60% of M. massiliense-PD patients, respectively. Symptomatic improvement was observed in all patients, and radiological improvement, including cavity amelioration or no deterioration, was observed in 42% and 70% of M. abscessus-PD and M. massiliense-PD patients, respectively. No resistance to clarithromycin or AMK was acquired.

Interpretation: IMIT with intermittent hospitalization can be a beneficial palliative treatment for refractory MAB-PD patients. This therapy alleviated symptoms, slowed radiological progression, and reduced the bacterial burden in some patients. However, radiological and microbiological responses by IMIT were more apparent in M. massiliense-PD than in M. abscessus-PD.

Open Forum Infect Dis 2022;9(10):ofac465

Clinical trial, Epetraborole

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A Study of Bedaquiline Administered as Part of a Treatment Regimen With Clarithromycin and Ethambutol in Adult Patients With Treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD)

ClinicalTrials.gov Identifier: NCT04630145

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status ⓘ : Recruiting
First Posted ⓘ : November 16, 2020
Last Update Posted ⓘ : September 13, 2023

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Clinical trial, Bedaquiline

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Study of Epetraborole in Patients With Treatment-refractory MAC Lung Disease

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Sponsor:

AN2 Therapeutics, Inc

Adequate antibiotic treatment generates survival benefits for NTM-PD patients

- not just the beginning of antibiotic therapy -

Impact of Time Between Diagnosis and Treatment for Nontuberculous Mycobacterial Pulmonary Disease on Culture Conversion and All-Cause Mortality

Check for updates

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]

erythrocyte sedimentation rate (ESR), and sex (BACES) system.

RESULTS: 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 severity, no association between the waiting period and 6-month culture conversion or death was identified. However, 6-month culture conversion demonstrated a significant negative correlation with death (crude hazard ratio [HR], 0.46, 95% CI, 0.33-0.65; adjusted HR, 0.51, 95% CI, 0.35-0.74). In the subgroup treated for more than 12 months, 12-month culture conversion was also associated with reduced death (adjusted HR, 0.51; 95% CI, 0.33-0.78).

INTERPRETATION: It may be reasonable to start antibiotics according to the "watchful waiting" strategy for NTM-PD, but given the survival benefits, achieving culture conversion is an important goal for patients in need of treatment.

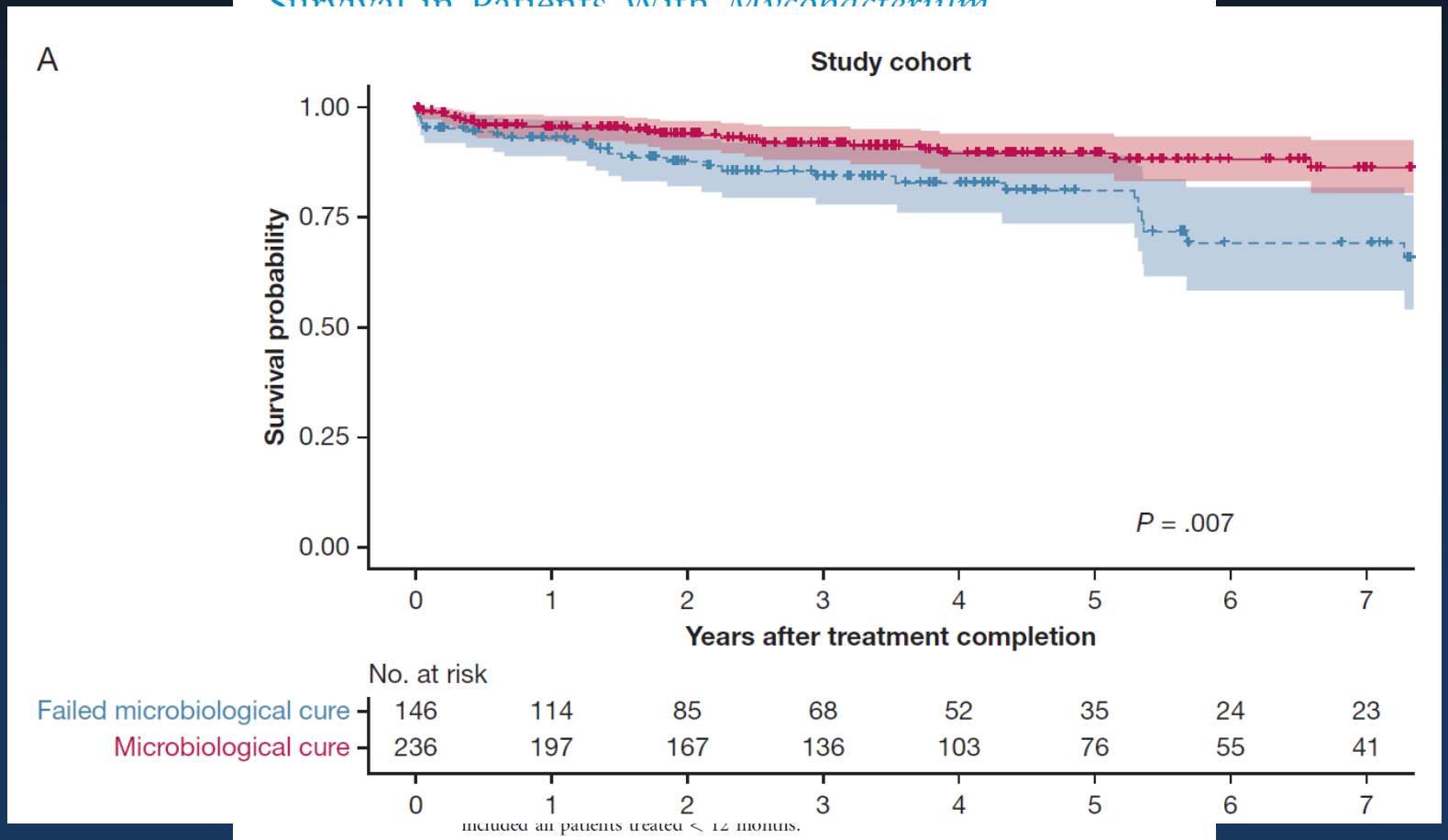
CHEST 2022; 161(5):1192-1200

Chest 2022;161(5):1192-120

Adequate antibiotic treatment generates survival benefits for NTM-PD patients

- not just the beginning of antibiotic therapy -

Microbiological Cure at Treatment Completion Is Associated With Longer Survival in Patients With *Mycobacterium*



Included all patients treated < 12 months.

Chest 2023;S0012-3692(23)00894-2

Adequate antibiotic treatment generates survival benefits for NTM-PD patients

- not just the beginning of antibiotic therapy -

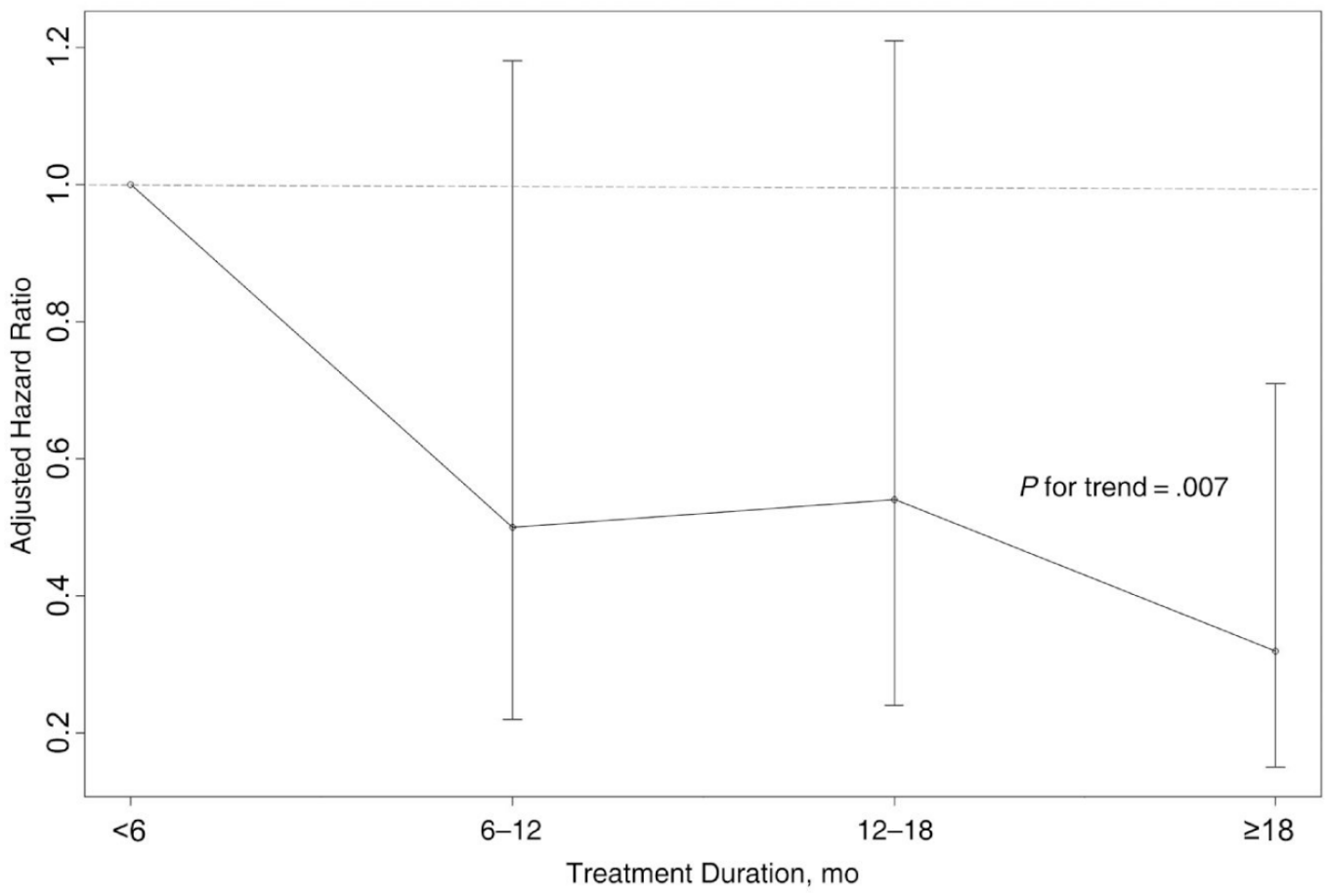


Figure 1. Changes in adjusted hazard ratios and 95% confidence intervals for mortality risk by treatment duration in patients with *Mycobacterium avium* complex pulmonary disease.

Clin Infect Dis 2023;77(1):120-126

Thank you