Two drugs (macrolide and ethambutol) are enough for non-cavitary nodular bronchiectatic MAC-PD

-Pro-

경북의대 이재희

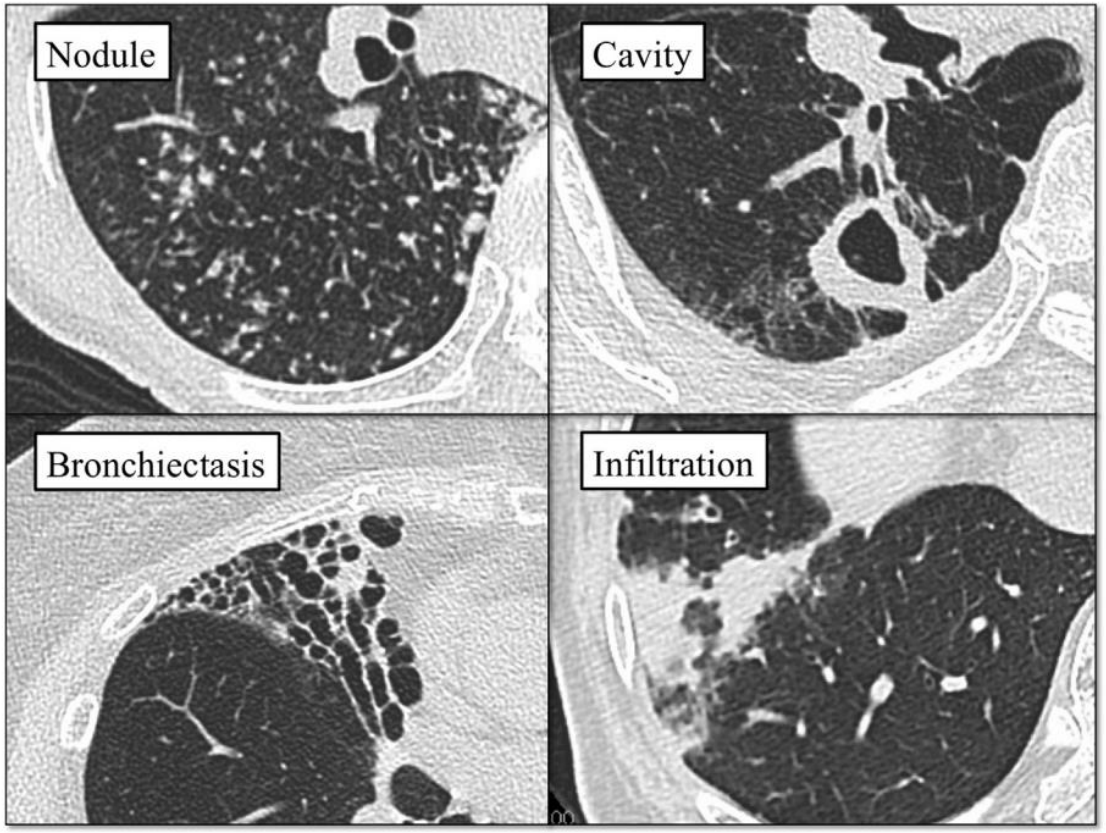
Diagnosis of NTM PD

Clinical criteria

Pulmonary or systemic symptoms

Radiological evidence

Four typical lesions on HRCT in MAC-PD



Urabe et al. J Infect Chemother 2018

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline 2020

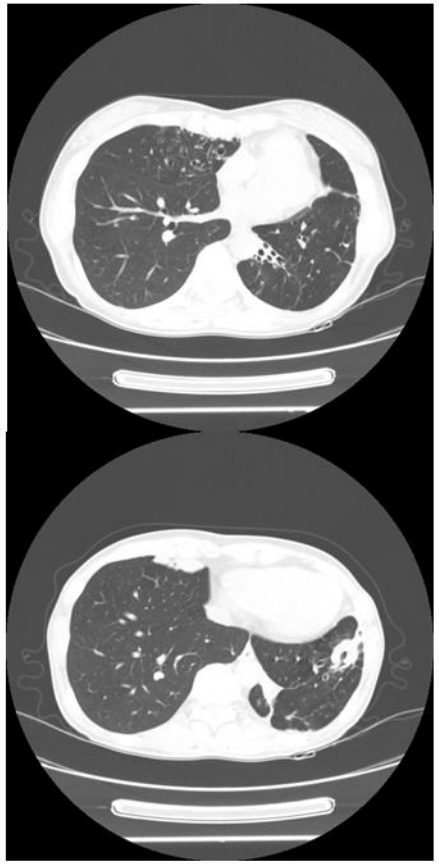
Radiologic types of MAC-PD

Fibrocavitary

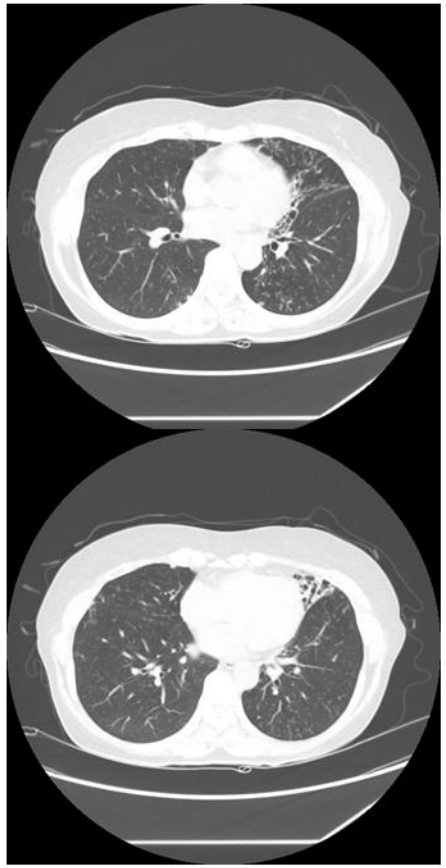
Nodular bronchiectatic (NB)

Unclassifiable

Cavitary NB

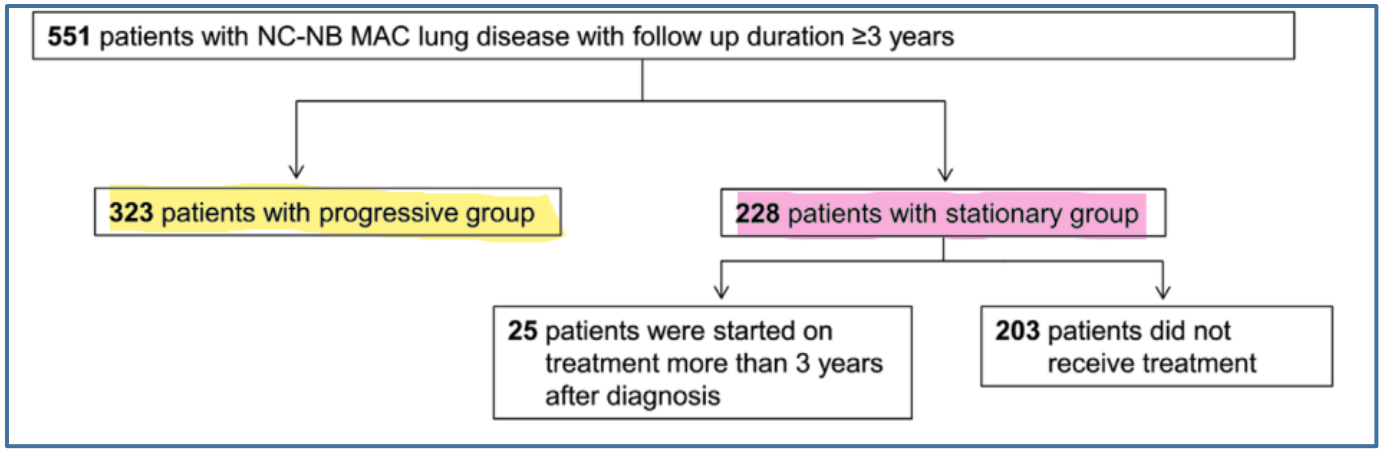


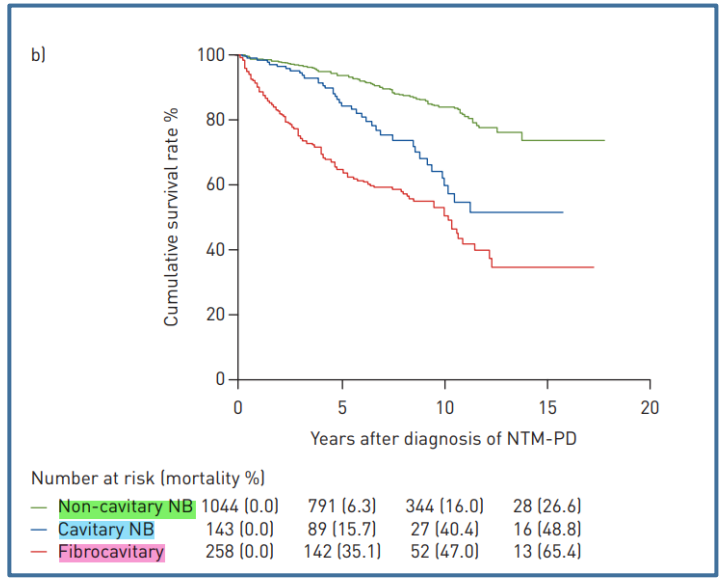
Non-cavitary NB



Disease course of non-cavitary nodular bronchiectatic MAC-PD

	Noncavitary NB	Cavitary NB	Fibrocavitary
Subjects	278 (58)	80 (17)	123 (25)
Time interval between diagnosis and treatment months	7.0 (2.2–23.2)	5.8 (1.5–16.6)	1.5 (0.5–5.4)
Treatment regimen¶			
Daily	135 (49)	80 (100)	123 (100)
Intermittent	143 (51)	0 (0)	0 (0)
Streptomycin	72 (26)	48 (60)	90 (73)
Duration months	3.0 (2.3–5.1)	3.2 (2.8–5.7)	4.0 (3.0–6.2)
Surgical resection+	11 (4)	5 (6)	20 (16)
Time from treatment start to resection months	21.9 (19.6–24.5)	12.7 (11.9–18.3)	12.6 (7.0–18.8)
Treatment duration months	19.7 (15.9–24.1)	24.0 (18.2–24.8)	24.1 (19.6–27.5)
Treatment outcomes			
Favourable	246 (88)	62 (78)	94 (76)
Unfavourable	32 (12)	18 (22)	29 (24)
Time to culture conversion months	1.2 (0.9–2.8)	2.0 (0.9–4.1)	3.2 (1.4–6.1)
Time from culture conversion to treatment completion months	16.3 (13.5–22.0)	17.2 (13.6–22.5)	18.2 (13.6–22.0)





Indolent course & favorable outcomes

Koh et al. Eur Respir J 2017

Kwon et al. Respiratory Medicine 2019

Jhun et al. Eur Respir J 2020

Treatment of MAC-PD by the presence of cavity

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)

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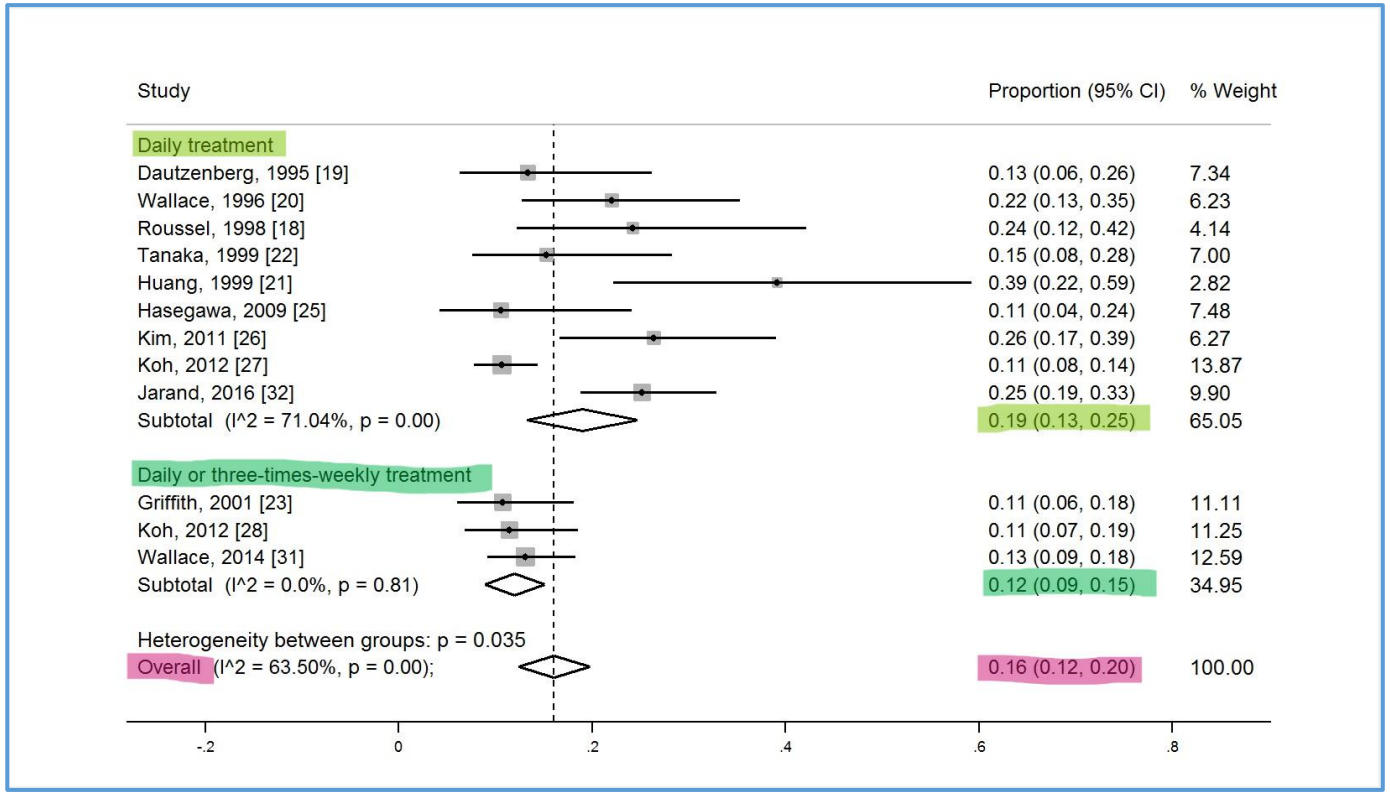
Default rate from macrolide-containing regimen in MAC-PD: meta-analysis



Proportion of discontinuation of treatment before 6-12mo/lost to follow-up for any reason

Kwak et al. CID 2017

Strategies for Enhancing Tolerance to MAC-PD treatment

- noncavitary nodular bronchiectatic subtype -

- Daily vs. intermittent administration
- Shortening of treatment duration
- Two drugs vs. three drugs

4. There have not been studies evaluating two- versus three-drug regimens for the treatment of MAC lung disease, but in general, two-drug regimens are not recommended because of concern about the development of macrolide resistance (293).

regimens for MAC lung disease. There are also concerns that a two-drug regimen for patients with cavitary MAC disease might promote the emergence of macrolide-resistant MAC isolates. Overall, clarithromycin or azithromycin with ethambutol on a daily basis would be acceptable for some patients (i.e., mild disease, medication intolerance, disease suppression) with nodular/bronchiectatic MAC disease. No other two-drug regimen is recommended (*see* the online supplement).

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases 2007

Two drugs (macrolide and ethambutol) are enough for non-cavitary nodular bronchiectatic MAC-PD

- Evidence for three-drug regimen recommended to treat MAC-PD
- Current evidence regarding two-drug versus three-drug regimens for MAC-PD
- Pharmacokinetic interaction between rifampin & macrolides
- Risk of development of macrolide-resistance in two-drug regimen

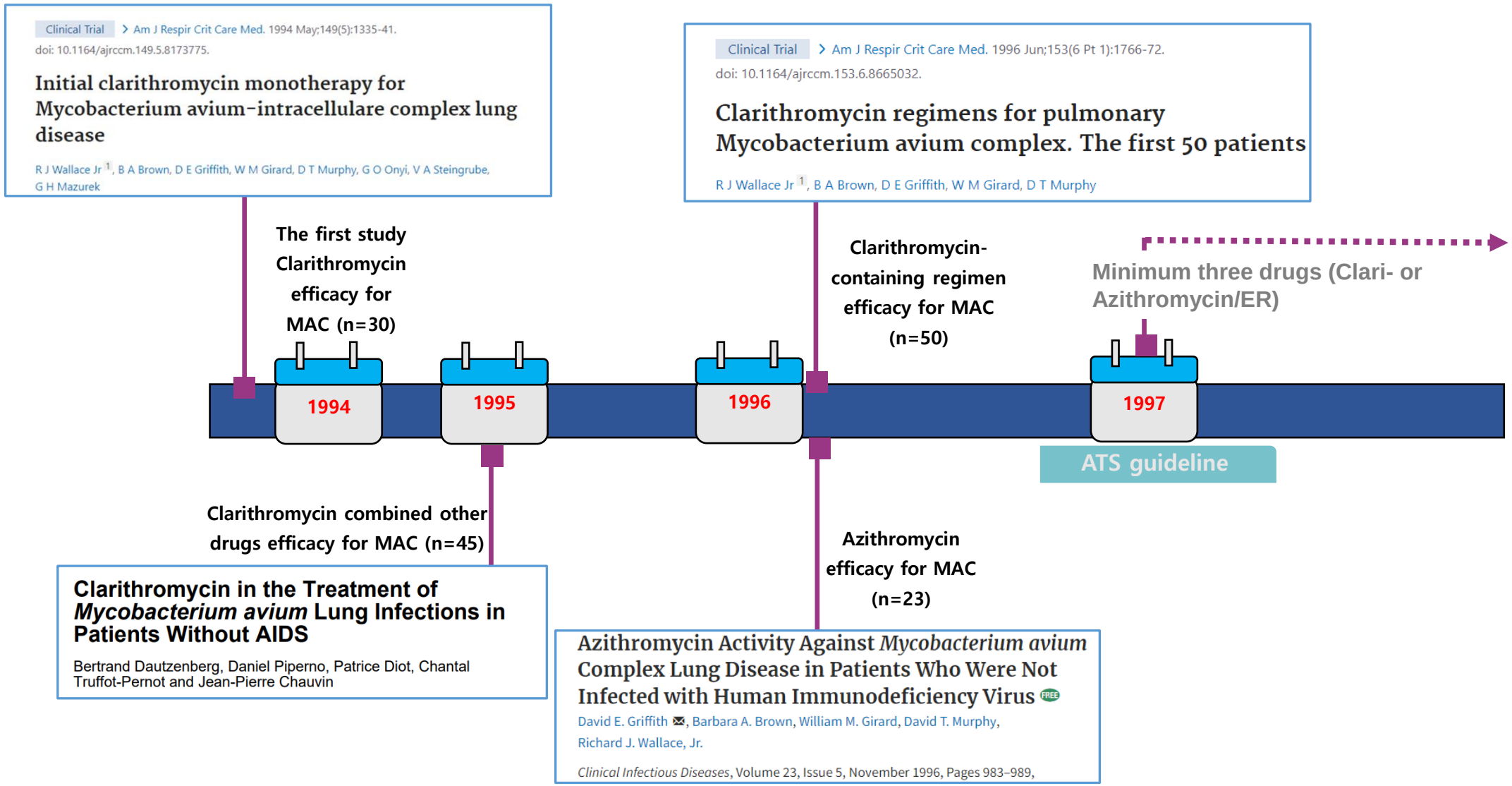
Why three-drug regimen for MAC-PD?

1. In patients with macrolide-susceptible MAC pulmonary disease, we suggest a treatment regimen with at least 3 drugs (including a macrolide and ethambutol) over a regimen with 2 drugs (a macrolide and ethambutol alone) (conditional recommendation, very low certainty in estimates of effect).

효과의 추정치에 대한 확신이 거의 없다. 실제효과는 효과의 추정치와 상당히 다를 것이다

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline 2020

Early non-comparator studies for efficacy of macrolides in MAC-PD



Five RCTs in HIV-neg MAC-PD population

Year/ Region	Population No.	Cavity	Regimens	Outcomes
2001/UK	75	~ 60%	REH vs RE	Treatment failure/relapse 16% vs 41%
2007/Japan	146	~ 55%	**REClari**Sm vs **REClari**	Culture conversion rate 72% vs 51%
2008/UK	170	~ 70%	**REClari** vs RECipro	Treatment failure/relapse 13% vs 23%
2011/Japan	27	N/A	**REClari** vs REGatiflo	Culture conversion 64% vs. 85%
2014/Japan	119	~50%	**REClari** vs **EClari**	Culture conversion 75% vs. 83%

MAC-PD treatment

1997

The newer macrolides are the cornerstone of contemporary therapy for pulmonary *M. avium* complex disease, as they are for disseminated *M. avium* complex disease. Initial therapy for adult HIV-negative patients with *M. avium* complex disease needing treatment should consist of a minimum three-drug regimen of clarithromycin (500 mg twice a day) or azithromycin (250 mg/d or 500 mg three times a week), rifabutin (300 mg/d) or rifampin (600 mg/d), and ethambutol (25 mg/kg per day for 2 mo followed by 15 mg/kg per day). For patients of

=

2020

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Two drugs vs. three drugs

A Randomized, Placebo-Controlled Study of Rifabutin Added to a Regimen of Clarithromycin and Ethambutol for Treatment of Disseminated Infection with *Mycobacterium avium* Complex

Fred M. Gordin, Paul M. Sullam, Stephen D. Shafran, David L. Cohn, Beverley Wynne, Linda Paxton, Kim Perry, C. R. Horsburgh, Jr. Author Notes

Clinical Infectious Diseases, Volume 28, Issue 5, May 1999, Pages 1080–1085,

Clinical Trial › Clin Infect Dis. 2003 Nov 1;37(9):1234-43. doi: 10.1086/378807. Epub 2003 Oct 3.

A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons with acquired immunodeficiency syndrome

Constance A Benson [1], Paige L Williams, Judith S Currier, Fiona Holland, Laura F Mahon, Rob Roy MacGregor, Clark B Inderlied, Charles Flexner, Judith Neidig, Richard Chaisson, Gerard F Notario, Richard Hafner; AIDS Clinical Trials Group 223 Protocol Team

Randomized Controlled Trial › Ann Am Thorac Soc. 2014 Jan;11(1):23-9. doi: 10.1513/AnnalsATS.201308-266OC.

Efficacy of clarithromycin and ethambutol for Mycobacterium avium complex pulmonary disease. A preliminary study

Seiichi Miwa [1], Masahiro Shirai, Mikio Toyoshima, Toshihiro Shirai, Kazumasa Yasuda, Koshi Yokomura, Takashi Yamada, Masafumi Masuda, Naoki Inui, Kingo Chida, Takafumi Suda, Hiroshi Hayakawa

Clinical Trial > Clin Infect Dis. 1999 May;28(5):1080-5. doi: 10.1086/514748.

A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with Mycobacterium avium complex

F M Gordin [1], P M Sullam, S D Shafran, D L Cohn, B Wynne, L Paxton, K Perry, C R Horsburgh Jr

- 47 sites (US, Canada, Mexico)
- HIV-positive, MAC bacteremia
- All patients: clarithromycin & ethambutol
- Rifabutin 300mg QD (n=102) & placebo (n=96)
- Primary endpoint: bacteriologic response at 16 wk (negative culture or ≥2-$\log_{10}$ decrease in cfu/mL)

Bacteriologic results of blood cultures

Endpoint variable	Rifabutin (n = 102)	Placebo (n = 96)	P value
Baseline			
Median cfu/mL (IQR)	18 (3–167)	24 (3–185)	.19
Week 8			
Bacteriologic response*	46/80† (58%)	47/81 (58%)	.95
Eradication	38/78 (49%)	36/68 (53%)	.61
Week 16			
Bacteriologic response*	44/70 (63%)	42/69 (61%)	.81
Eradication	40/55 (73%)	37/51 (73%)	.98

Time to bacteriologic response

	Rifabutin	Placebo	P value
Bacteriologic response	30 d	56 d	0.470
Eradication	55 d	64 d	0.320

Adverse events

	Rifabutin	Placebo	P value
Leukopenia (<1,000/mm^3)	18%	8%	<0.05

Clinical Trial > Clin Infect Dis. 2003 Nov 1;37(9):1234-43. doi: 10.1086/378807. Epub 2003 Oct 3.

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- **Multicenter, open-label**
- **HIV (+) disseminated MAC**
- **Clarithromycin+ethambutol (n=53) vs. Clarithromycin+rifampicin (n=50) vs. Clarithromycin+ethambutol+rifampicin (n=57)**
- **Primary end point: complete microbiological (+clinical) response at 12wk (2 consecutive blood culture-negativity/afebrile & alive)**

Microbiological responses

Response, week	No. (%) of patients in indicated treatment arm			P^a
	C+E	C+R	C+E+R	
Complete microbiologic				
6	16 (30)	10 (20)	15 (26)	.497
8	20 (38)	17 (34)	20 (35)	.935
12	21 (40)	21 (42)	29 (51)	.454
16	25 (47)	23 (46)	36 (63)	.130
Complete microbiologic and clinical				
6	10 (19)	7 (14)	11 (19)	.755
8	9 (17)	12 (24)	13 (23)	.653
12	14 (26)	13 (26)	17 (30)	.903
16	11 (21)	12 (24)	21 (37)	.144

Randomized Controlled Trial > Ann Am Thorac Soc. 2014 Jan;11(1):23-9.
doi: 10.1513/AnnalsATS.201308-266OC.

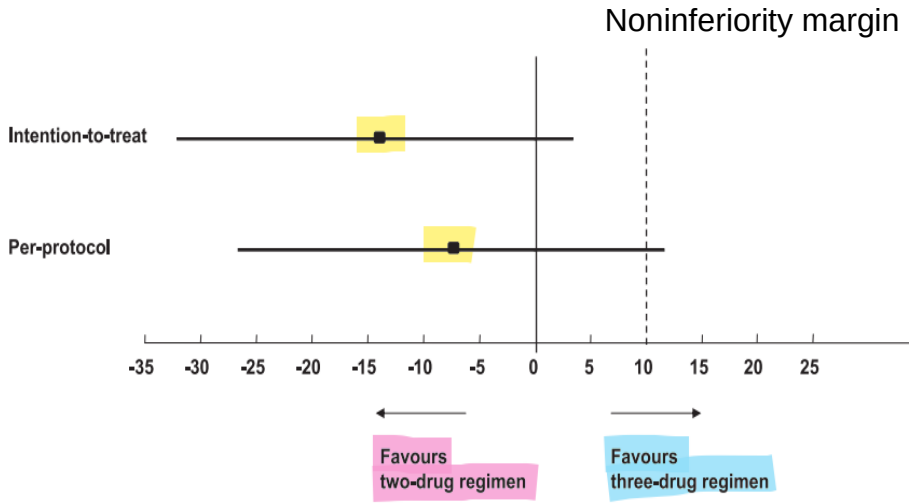
Efficacy of clarithromycin and ethambutol for Mycobacterium avium complex pulmonary disease. A preliminary study

Seiichi Miwa [1], Masahiro Shirai, Mikio Toyoshima, Toshihiro Shirai, Kazumasa Yasuda, Koshi Yokomura, Takashi Yamada, Masafumi Masuda, Naoki Inui, Kingo Chida, Takafumi Suda, Hiroshi Hayakawa

- Japan, 2014
- HIV(-) MAC PD
- All patients: clarithromycin (600mg) & ethambutol (750mg)
- Rifampicin (450mg) (n=59) & placebo (n=60)
- Cavitary lesion (49% [3-drug] vs. 47% [2-drug])
- Primary endpoint: sputum culture negative conversion *3 at 12 mo (ITT)

Sputum negative conversion rate

	Rifampicin	Placebo	Difference
ITT	41%	55%	-14.4% [95% CI, -32.1~3.4%]
PP	75%	83%	-7.5% [95% CI, -26.6~11.6%]



Sputum negative conversion rate in patients with cavitary disease (PP)

Rifampicin	Placebo	P value
11/15 (73%)	11/16 (68%)	NS

Randomized Controlled Trial > Ann Am Thorac Soc. 2014 Jan;11(1):23-9.
doi: 10.1513/AnnalsATS.201308-266OC.

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- Primary endpoint: sputum culture negative conversion *3 at 12 mo (ITT)

Time to sputum negative conversion

Rifampicin	Placebo	P value
3.2 m	4.1 m	0.297

Adverse events

Adverse Event	Three-Drug Regimen (Clarithromycin, Ethambutol, and Rifampicin) (*N = 59*)	Two-Drug Regimen (Clarithromycin and Ethambutol) (*N = 60*)
Discontinuation of study drugs	22 (37.2)	16 (26.6)
Loss of appetite	6 (10.1)	1 (1.6)
Nausea	2 (3.3)	3 (5.0)
Diarrhea	1 (1.6)	2 (3.3)
Stomatitis	4 (6.7)	4 (6.6)
Rash	8 (13.5)	9 (15.0)
Fever	4 (6.7)	5 (8.3)
Visual impairment	3 (5.0)	1 (1.6)
Hepatitis	1 (1.6)	2 (3.3)
Headache	2 (3.3)	1 (1.6)
Pancytopenia	2 (3.3)	0 (0)
Others	6 (10.1)	1 (1.6)

2 versus 3-drug regimen to treat Mycobacterium avium complex infection: a systematic review and meta-analysis

Dong Nguyen Van, Hai Duong, Ming-Chia Lee, Chih-Hsin Lee

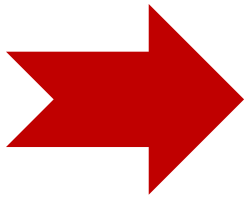
European Respiratory Journal 2023 62: OA866; **DOI:** 10.1183/13993003.congress-2023.OA866

Combined prolonged treatment is required to treat Mycobacterium avium complex (MAC) infections. However, whether the 2-drug regimen is inferior to the 3-drug regimen is still being determined.

A systematic review and meta-analysis were conducted to compare the efficacy of the two treatments regarding bacteriology responses, mortality, and acquired macrolide resistance. Randomized controlled trials (RCT), which compared two-drug and three-drug regimens published in English before December 2022, were eligible.

Six electronic databases were searched: PubMed, Cochrane Library, EMBASE, Scopus, Google Scholar, and Global Health Library. We identified 2253 studies, but only seven RCTs encompassing 724 patients were eligible for inclusion in this meta-analysis.No significant differences between the two treatments were detected when all 7 RCT studies reported bacteriologic responses were pooled (724 patients, OR=0.83, 95%CI:0.51-1.35). Regarding macrolide resistance, six studies, including 671 patients (329 with the 2-drug regimen, 342 with the 3-drug regimen), showed no significant differences between the two treatments (RD=0.06, 95%CI: -0.01 – 0.13). Five RCTs studies reported mortality, including 553 patients (301 with the 2-drug regimen, 252 with the 3-drug regimen). One of them had no events in both arms. Four remaining studies showed no significant differences between the 2-drug and 3-drug regimens (OR=1.06, 95%CI: 0.45 – 2.52, p=0.89).

The findings suggest that when choosing an initial regimen for MAC infection treatment, a 2-drug regimen may be appropriate. Further RCT might be needed to confirm this result.



Seven RCTs (n=724)
Bacteriologic response

Six RCTs (n=671)
Macrolide resistance

Five RCTs (n=553)
Mortality

2-drug vs 3 drug regimens:
no significance difference

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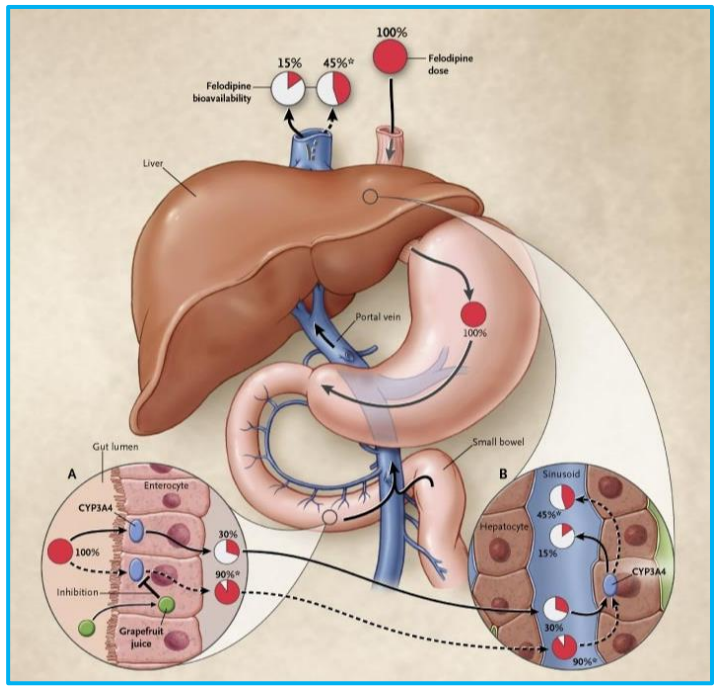
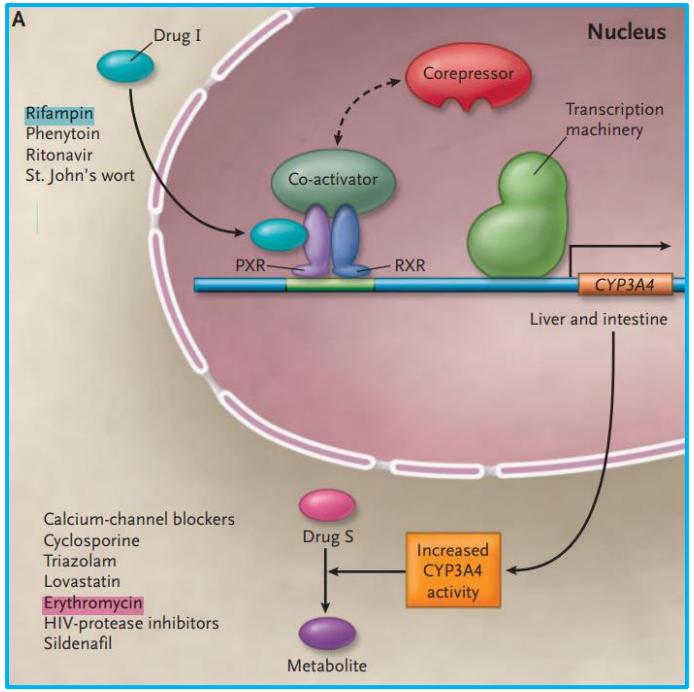
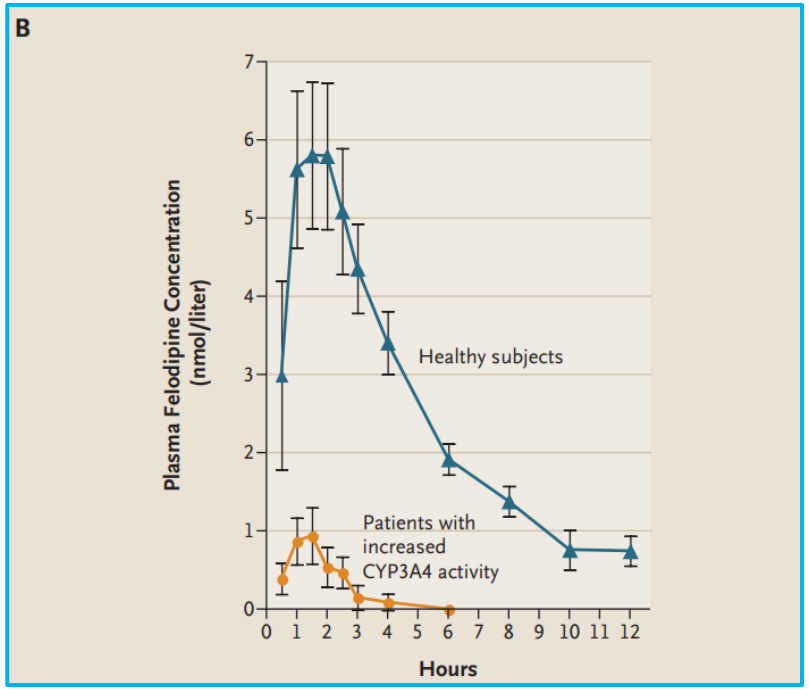
Rifampin: friend or foe?







CYP3A Inducer: Rifamycin ⟷ **CYP3A substrate: Macrolide**

Grant Wilkinson. N Engl J Med 2005

Efficacy of Clarithromycin and Ethambutol for *Mycobacterium avium* Complex Pulmonary Disease

A Preliminary Study

Seiichi Miwa[1,2], Masahiro Shirai[1,2], Mikio Toyoshima[2], Toshihiro Shirai[2], Kazumasa Yasuda[2], Koshi Yokomura[2], Takashi Yamada[2], Masafumi Masuda[2], Naoki Inui[2], Kingo Chida[2], Takafumi Suda[2], and Hiroshi Hayakawa[1,2]

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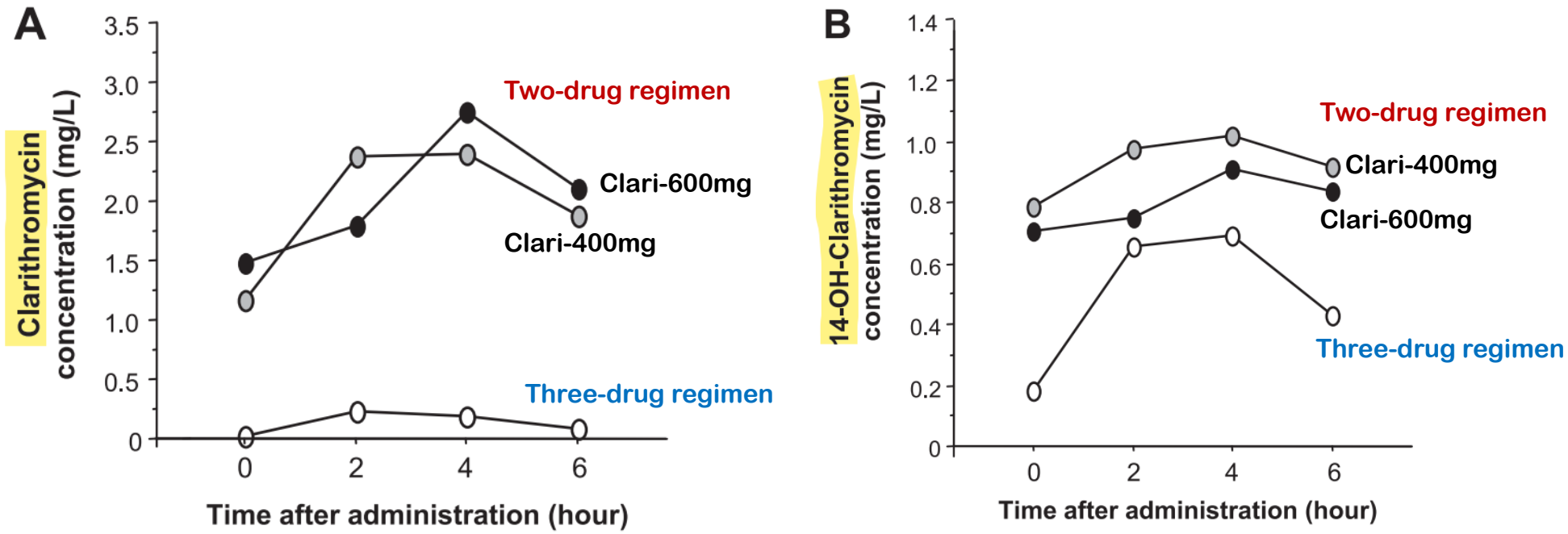

Mean concentration of clarithromycin & 14-hydroxyl-clarithromycin

Macrolides: Pharmacokinetic interactions with rifampicin

Drug		Without a Rifamycin	With Rifampicin	% Change, *P* Value
Clarithromycin	AUC (mg · h/L)	19.74 ± 9.18 (n = 18)	5.32 ± 3.87 (n = 39)	−73%, $P < 0.001$
	C_{max} (μg/ml)	3.91 ± 1.86 (n = 18)	1.25 ± 0.91 (n = 39)	−68%, $P < 0.001$
	C_{last} (μg/ml)	2.61 ± 1.63 (n = 18)	0.48 ± 0.39 (n = 39)	−82%, $P < 0.001$
Azithromycin	AUC (mg · h/L)	1.70 ± 1.19 (n = 94)	1.30 ± 0.80 (n = 272)	−24%, $P < 0.001$
	C_{max} (μg/ml)	0.35 ± 0.26 (n = 94)	0.27 ± 0.18 (n = 272)	−23%, $P = 0.007$
	C_{last} (μg/ml)	0.22 ± 0.19 (n = 94)	0.15 ± 0.09 (n = 272)	−32%, $P = 0.001$

van Ingen et al. Am J Respir Crit Care Med 2012

Association between C_{max} of antibiotics and microbiological response

Therapy type	C_{max} (μg/ml) by drug[b]	Favorable responses	Unfavorable responses	Univariate analysis OR (95% CI)	Univariate analysis P	Multiple logistic regression[c] aOR (95% CI)	Multiple logistic regression[c] 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
	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

Jeong et al. Antimicrobial Agents and Chemotherapy 2016

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Acquired macrolide resistance

Clinical Trial > Am J Respir Crit Care Med. 1994 May;149(5):1335-41.
doi: 10.1164/ajrccm.149.5.8173775.

Initial clarithromycin monotherapy for Mycobacterium avium–intracellulare complex lung disease

R J Wallace Jr [1], B A Brown, D E Griffith, W M Girard, D T Murphy, G O Onyi, V A Steingrube, G H Mazurek

- **Clarithromycin 500mg BID for 4Mo**
- **16% => clarithromycin resistance**

18, 161]. A 2-drug regimen including a macrolide and ethambutol is the regimen with the fewest possible drugs for treating MAC. The role of a rifamycin, or another third drug, is unregimen [161]. Until additional evidence is provided showing that acquired macrolide resistance is equally common among macrolide containing 3-drug and 2 drug regimens, the panel prefers a 3-drug regimen. A PCORI-funded randomized con-

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline 2020

Clinical Trial > Clin Infect Dis. 1999 May;28(5):1080-5. doi: 10.1086/514748.

A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with Mycobacterium avium complex

F M Gordin [1], P M Sullam, S D Shafran, D L Cohn, B Wynne, L Paxton, K Perry, C R Horsburgh Jr

- 47 sites (US, Canada, Mexico)
- HIV-positive, MAC bacteremia
- All patients: clarithromycin & ethambutol
- Rifabutin 300mg QD (n=102) & placebo (n=96)
- Primary endpoint: bacteriologic response at 16 wk (negative culture or ≥2-$\log_{10}$ decrease in cfu/mL)

Resistance to clarithromycin during Tx

	Rifabutin	Placebo	P value
Total	7/70 (10%)	10/69 (14%)	NS
16wk-bacteriologic response (-)	6/26 (23%)	4/27 (15%)	NS
16wk-bacteriologic response (+)	1/44 (2%)	6/42 (14%)	0.055

Only one => relapse at week 40

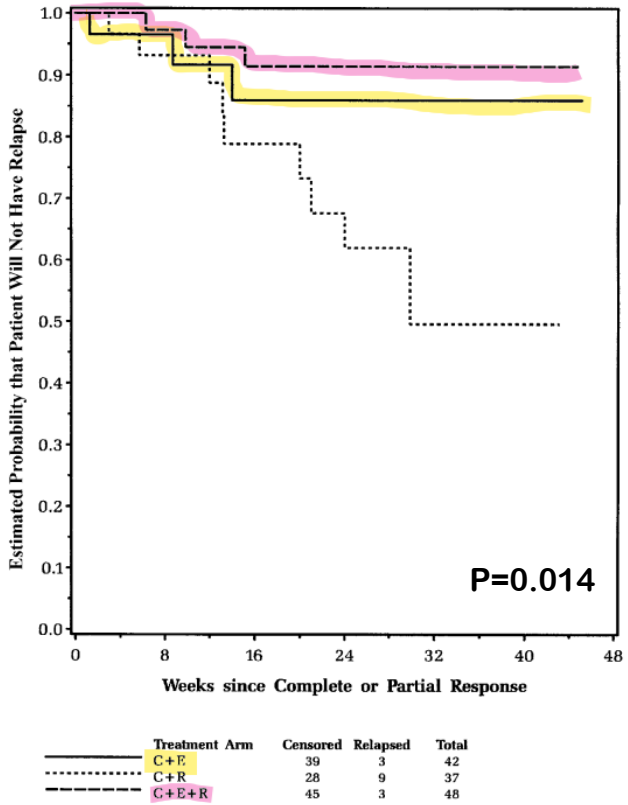
Clinical Trial > Clin Infect Dis. 2003 Nov 1;37(9):1234-43. doi: 10.1086/378807. Epub 2003 Oct 3.

A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons with acquired immunodeficiency syndrome

Constance A Benson [1], Paige L Williams, Judith S Currier, Fiona Holland, Laura F Mahon, Rob Roy MacGregor, Clark B Inderlied, Charles Flexner, Judith Neidig, Richard Chaisson, Gerard F Notario, Richard Hafner; AIDS Clinical Trials Group 223 Protocol Team

- Multicenter, open-label
- HIV (+) disseminated MAC
- Clarithromycin+ethambutol (n=53) vs. Clarithromycin+rifampicin (n=50) vs. Clarithromycin+ethambutol+rifampicin (n=57)
- Primary end point: microbiological (+clinical) response at 12 wk

Time to relapse



P=0.057

Clarithromycin- resistant MAC in relapse cases

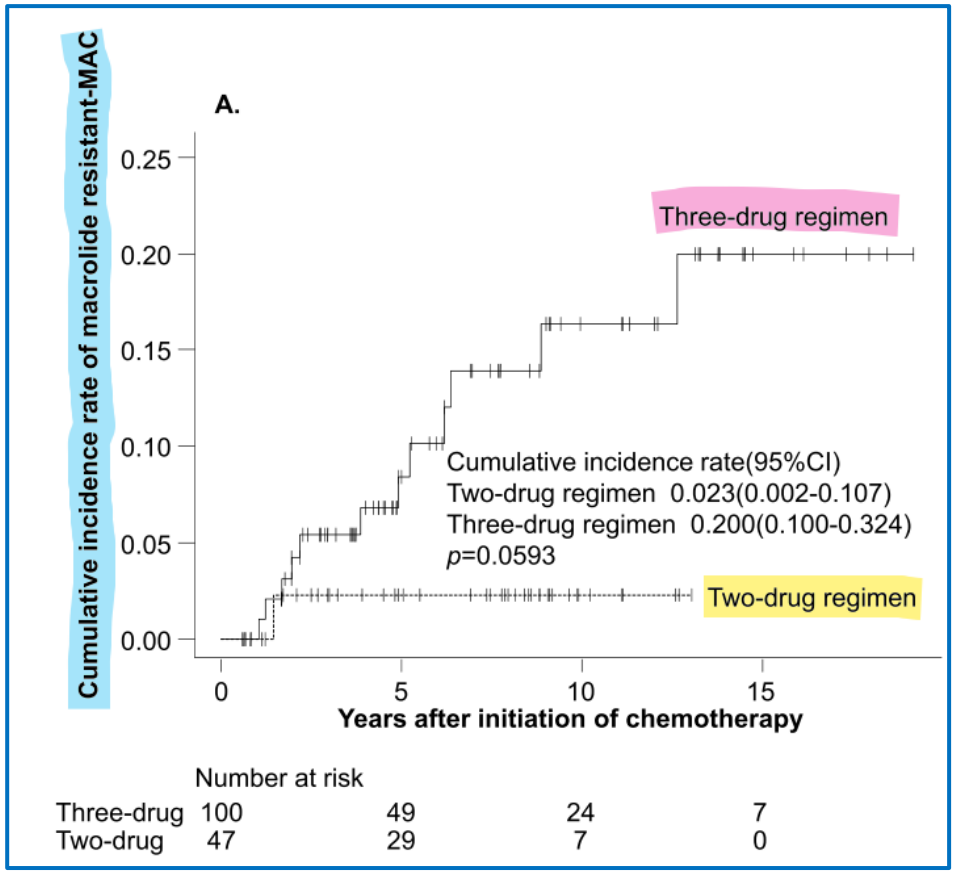
CER	CE	CR
1/3	1/3	7/9

HIV(-) MAC-PD

Macrolides resistance: Two-drug vs. three drug regimen

	All patients (n = 147)	Two-drug regimen (CE) (n = 47)	Three-drug regimen (CER) (n = 100)	p value
Female sex, No. (%)	104 (70.8)	33 (70.2)	71 (71.0)	1
Age at diagnosis, median (IQR)	72 (62–79)	73 (66–80.5)	71 (61.75–78.25)	0.278
Species				
Mycobacterium avium	77 (52.3)	27 (57.4)	50 (50.0)	0.479
Mycobacterium intracellulare	79 (53.7)	25 (53.2)	54 (54.0)	1
Sputum AFB smear positive	73 (49.7)	23 (48.9)	50 (50.0)	1
Radiological findings				
Fibrocavitary type	39 (26.5)	11 (23.9)	28 (28.0)	0.689
Nodular bronchiectatic type	103 (70.0)	34 (72.3)	69 (69.0)	0.847
Solitary nodule	5 (3.4)	2 (4.3)	3 (3.0)	0.655
Cavity (detected by HRCT)	53 (36.1)	15 (31.9)	38 (38.0)	0.581
Discontinuation of the initial chemotherapy within 2 months	34 (23.1)	3 (6.4)	31 (31.0)	<0.01
Sputum conversion at 12 months after initiation of chemotherapy *	61 (41.5)	24 (51.1)	37 (37.0)	0.111
Development of macrolide-resistant MAC	13 (8.8)	1 (2.1)	12 (12.0)	0.0621

With cavity



Yasuhiro Ito et al. Respiratory Medicine 2020

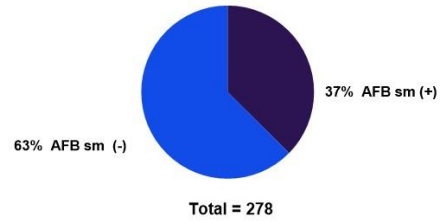
Risk of macrolides resistance & bacterial load

Univariable analysis for macrolide-resistance risk

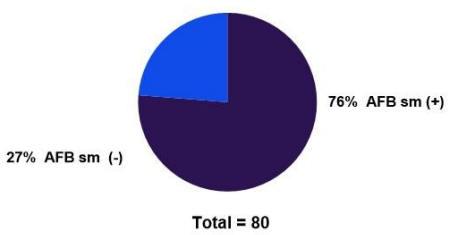
	HR	95% CI	p value
Male	1.616	0.5147–5.071	0.41
Age >73 yr	1.277	0.431–3.784	0.66
Species			
Mycobacterium avium	1.726	0.5298–5.624	0.37
Mycobacterium intracellulare	0.4211	0.1282–1.383	0.15
Comorbidity			
Respiratory disease	1.037	0.2881–3.733	0.96
Old tuberculosis	1.756	0.417–7.398	0.44
Systemic disease	0.4392	0.1528–1.263	0.13
Cardiovascular disease	0.5186	0.1143–2.352	0.39
Diabetes mellitus	0.8991	0.1088–7.43	0.92
Gastrointestinal disease	0.3373	0.04245–2.68	0.3
Sputum AFB smear positive	14.28	2.039–100	<0.01
Radiological findings			
Fibrocavitary type	3.793	1.295–11.12	0.015
Nodular bronchiectatic type	0.325	0.1105–0.9558	0.041
Cavity (detected by HRCT)	4.603	1.433–14.78	0.01
BMI <18.7 kg/m^2	8.799	1.091–70.99	0.041
Bloody sputum, hemoptysis	4.131	1.309–13.04	0.016
WBC > 8500/μL [a]	3.5527	1.004–12.39	0.049
ALB < 4.0 g/dL [b]	3.702	1.248–10.98	0.018
CRP >0.3 mg/dL [c]	14.15	3.35–59.73	<0.01
Initial two-drug regimen (CE)	0.1756	0.02218–1.390	0.099
Macrolide monotherapy over a month	1.255	0.2731–5.767	0.77
Discontinuation of the initial chemotherapy within 2 months	1.065	0.2934–3.864	0.92
Duration of total therapy > 26.7 months	0.6862	0.2536–1.857	0.46
Multiple regimens (two or more)	0.8702	0.2853–2.654	0.81

Yasuhiro Ito et al. Respiratory Medicine 2020

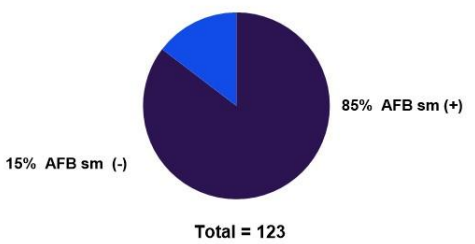
Initial sputum AFB smear at the start of treatment



Non-cavitary NB



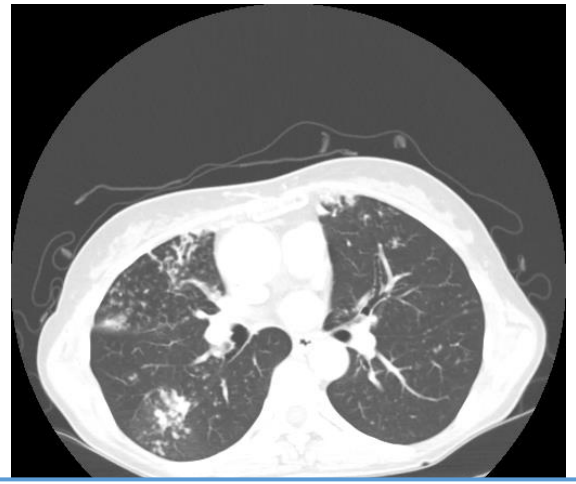
Cavitary NB

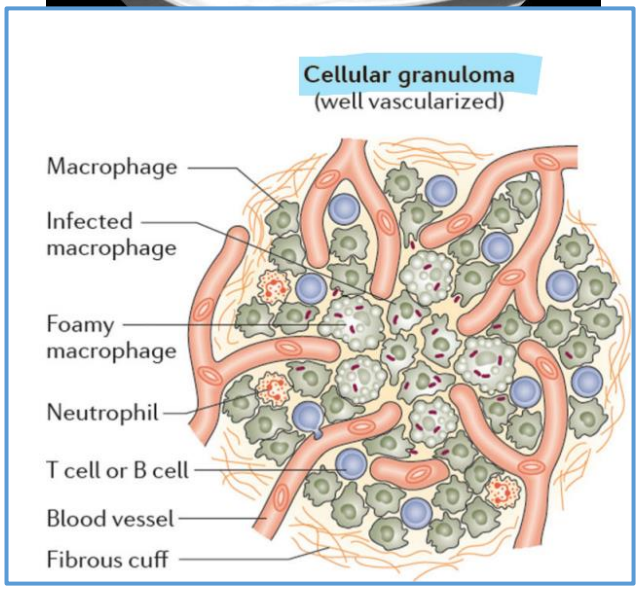


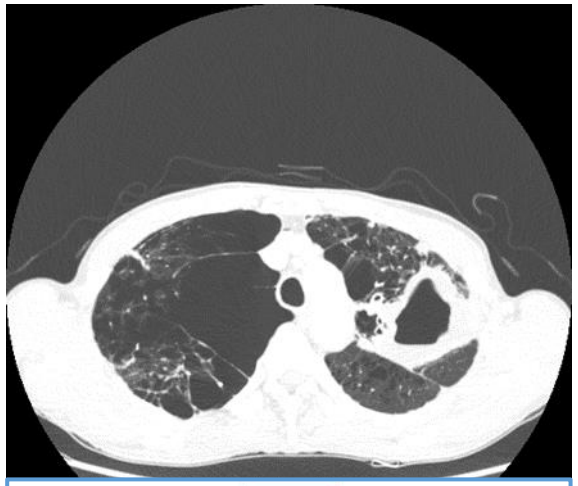
Fibrocavitary

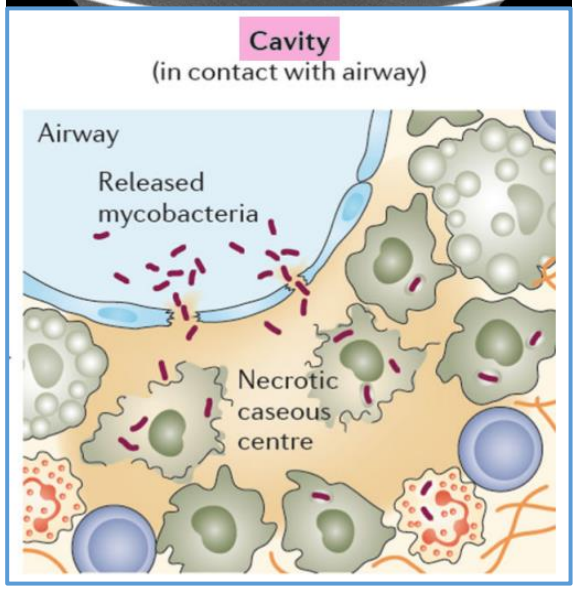
Koh et al. Eur Respir J 2017

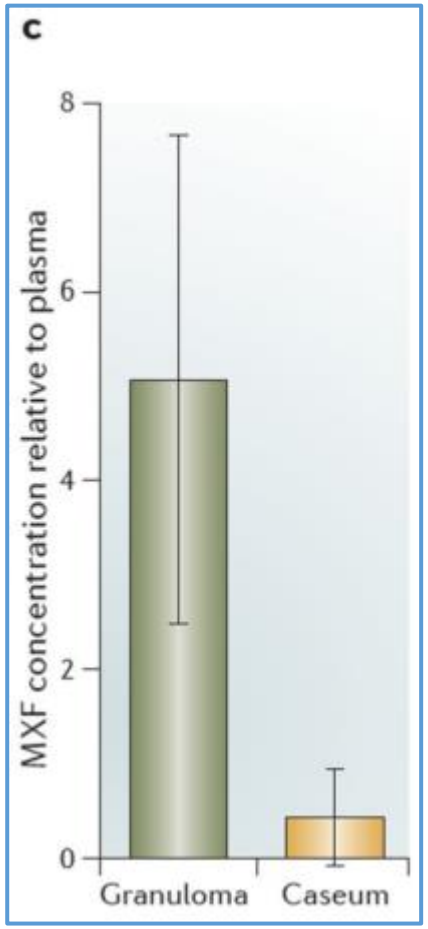
The path of anti-TB drugs: from blood to lesions











Veronique Dartois Nat Rev Microbiol. 2014

RECRUITING

Comparison of Two- Versus Three-antibiotic Therapy for Pulmonary Mycobacterium Avium Complex Disease (MAC2v3)

ClinicalTrials.gov ID NCT03672630

Sponsor Kevin Winthrop

Information provided by Kevin Winthrop, Oregon Health and Science University (Responsible Party)

Eligibility Criteria

Description

Inclusion Criteria:

- Culture positive pulmonary MAC meeting ATS/IDSA disease criteria
- Age over 18 years
- Ability to provide informed consent

Exclusion Criteria:

- Fibrocavitary disease

Project End Date: Sep 2026

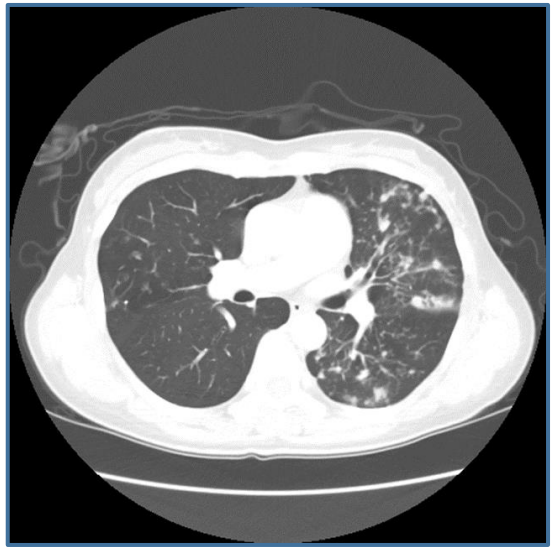
Design Elements	Description
Design	Randomized controlled trial
Population	500 adults ages 18 and older with pulmonary MAC disease
Interventions/ Comparators	• 2-drug regimen (azithromycin and ethambutol) • 3-drug regimen (azithromycin, ethambutol, and rifampin)
Outcomes	Primary: acid-fast bacilli culture negativity, therapy completion with satisfactory adherence (defined as taking 80% of prescribed doses or not missing more than 75 days of treatment taken three times per week) Secondary: respiratory symptoms, quality of life, fatigue, gastrointestinal symptoms, liver function, macrolide resistance
Timeframe	1-year follow-up for primary outcomes

Two drugs (macrolide and ethambutol) are enough for non-cavitary nodular bronchiectatic MAC-PD

A less severe phenotype

Evidence for three-drug regimen recommended to treat MAC-PD: A few

Pharmacokinetic interaction between rifampin & macrolides: disadvantageous



Evidence regarding efficacy between two-drug and three-drug regimens for MAC-PD: not inferior

Risk of development of macrolide-resistance in two-drug regimen: not elevated

Rebuttal to the counterargument

Two drugs (macrolide and ethambutol) for NC-NB MAC-PD

Point of view: Cons

- No RCT regarding 2-drug vs 3-drug regimen in NC-NB MAC-PD

Point of view: Pros

- No efficacy difference in studies regarding 2-drug vs 3-drug regimen in cases with more severe MAC infection => why not 2-drug in a less severe phenotype?

NC-NB MAC PD:
Intermittent 3-drug regimen vs. daily 2-drug regimen

	Intermittent 3-drug	Daily 2-drug	Dose difference exposed during a week
Clarithromycin	1000mg*3	1000mg*7	+4000mg
Azithromycin	500mg*3	250mg*7	+250mg
Ethambutol	25mg/kg*3	15mg/kg*7	+30mg/kg (eg BW=50kg, 1,500mg)
Rifampicin	600mg*3	-	-1800mg

Standard regimen of daily 3-drug regimen: limited efficacy & intolerance problem

Intermittent 2-drug regimen (azithromycin & EMB) in patients with non-cavitary MAC PD
: 76% of sputum culture conversion (at 12Mo) [by Moon et al. Antimicrob Agents Chemother 2019]

Daily 2-drug regimen: higher exposure of key drugs (macrolide & ethambutol) for MAC pathogen
better tolerability

Two drugs (macrolide and ethambutol) for NC-NB MAC-PD

Point of view: Cons

- Unexpected monotherapy in cases with drug intolerance or resistance

Point of view: Pros

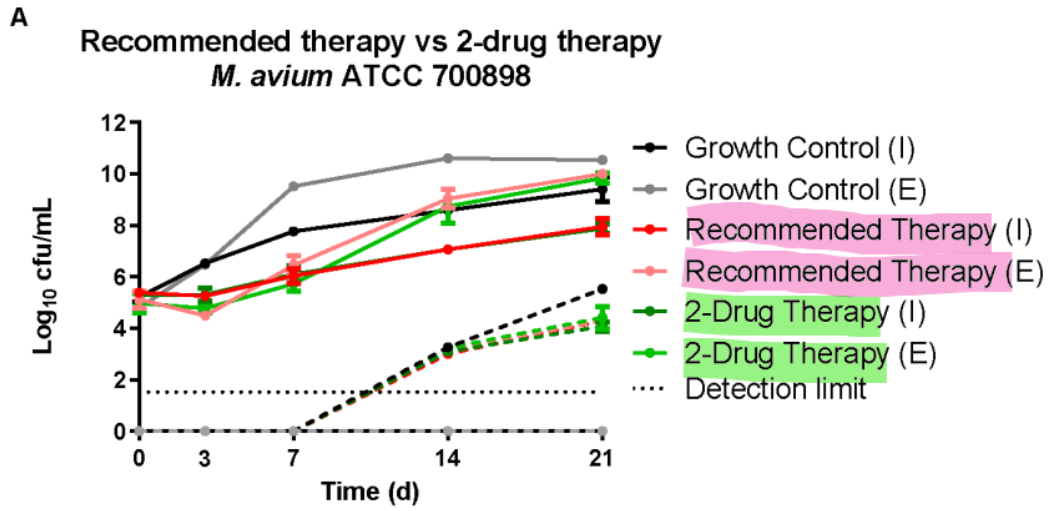
- This story pertains to the initial treatment for macrolide-susceptible NC-NB MAC PD
- Probability of drug intolerance is not higher in 2-drug regimen
- Elevated risk of macrolide-resistance MAC development in NC-NB MAC PD cases receiving macrolide and ethambutol concurrently: doubtful

› Antimicrob Agents Chemother. 2023 Nov 15;67(11):e0087423. doi: 10.1128/aac.00874-23. Epub 2023 Oct 25.

The role of rifampicin within the treatment of *Mycobacterium avium* pulmonary disease

Jodie A Schildkraut [# 1], Jelmer Raaijmakers [# 1], Rob Aarnoutse [2], Wouter Hoefsloot [3], Heiman F L Wertheim [1], Jakko van Ingen [1]

- In vitro hollow fiber model (NB-MAC PD)
- Azithromycin-ethambutol-rifampicin vs. azithromycin-ethambutol
- THP-1 cells infected with *M.avium* ATCC700898 (21d)

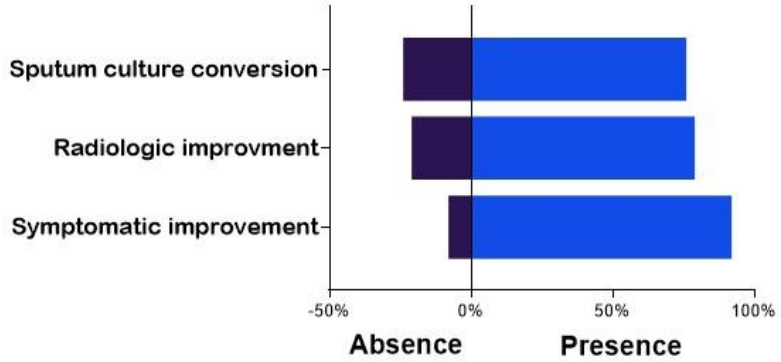


› Antimicrob Agents Chemother. 2019 Dec 20;64(1):e01787-19. doi: 10.1128/AAC.01787-19. Print 2019 Dec 20.

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

Seong Mi Moon [1], In Young Yoo [2], Hee Jae Huh [2], Nam Yong Lee [2], Byung Woo Jhun [3]

- 38 patients with non-cavitary MAC-PD
- Intermittent azithromycin & ethambutol for ≥12mo



No additional macrolide-resistance

Two drugs (macrolide and ethambutol) for NC-NB MAC-PD

Point of view: Cons

- Insufficient data regarding correlation between serum macrolide exposure and clinical outcome

Point of view: Pros

- Confounding variables not considered
- Definite evidence about lower macrolide exposure associated with use of rifamycin
- The higher antibiotic-exposure, the less antibiotic-resistance

제135차 대한결핵 및 호흡기학회
춘계학술대회 2023

2023년 4월 8일(토) 여수엑스포컨벤션센터

Oral Shorter Regimen for MDR-TB in Korea

1. Pro
2. Con

경청해주셔서 감사합니다